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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

AMGEN, INC. Plaintiff, v. SANDOZ INC., et al. Defendants.	**Civil Action No. 18-11026 (MAS)(DEA) (consolidated)** [redacted]

DEFENDANTS' PROPOSED FINDINGS OF FACT

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TABLE OF ABBREVIATIONS

Term	Definition
’358 patent	U.S. Patent No. 6,020,358
’638 patent	U.S. Patent No. 7,427,638
’536 patent	U.S. Patent No. 8,455,536
’101 patent	U.S. Patent No. 7,893,101
’283 patent	U.S. Patent No. 8,093,283
’541 patent	U.S. Patent No. 10,092,541
’515 application	U.S. Provisional Application No. 60/366,515
’052 publication	U.S. Patent Publication No. 2003/0187052
Amgen	Plaintiff Amgen Inc.
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
Apremilast	(+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione
Brittain 1997	Brittain, H.G., “Spectral Methods for the Characterization of Polymorphs and Solvates,” *Journal of Pharmaceutical Sciences* (1997)
Brittain 1999	H.G. Brittain, *Methods for the Characterization of Polymorphs*, Polymorphism in Pharmaceutical Solids, part of the Drugs and the Pharmaceutical Sciences collection, Vol. 95, pp. 227-278 (H. Brittain ed., 1999)
Byrn 1994	S.R. Byrn et al., Solid-State Pharmaceutical Chemistry, Chem. Mater. 6:1148-1158 (1994)
Byrn 1995	S. R. Byrn et al., “Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations,” *Journal Pharmaceutical Research*, 12(7): 945-54 (1995)
cAMP	Adenosine 3′,5′-cyclic monophosphate
Celgene	Celgene Corp.

Term	Definition
DDX	Defendants' demonstratives
DDX-ZYDUS	Defendant Zydus' demonstratives
Defendants	Defendants Sandoz Inc., and Zydus Pharmaceuticals (USA) Inc.
DFF	Defendants' proposed findings of fact
DSC	Differential scanning calorimetry
DTC	Direct to consumer
DTX	Defendants' trial exhibit
DVS	Dynamic vapor sorption
Dyke 1999	Dyke et al., "The therapeutic potential of PDE4 inhibitors," *Expert Opin. Invest. Drugs*, 8(9): 1301-25 (1999)
EPO	European Patent Office
FDA	U.S. Food and Drug Administration
Fieser	Louis F. Fieser & Kenneth L. Williamson, *Crystallization*, *in* Organic Experiments, pp. 43-53 (3rd ed. 1975)
Guillory	J. K. Guillory, *Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids*, Polymorphism in Pharmaceutical Solids, part of the Drugs and the Pharmaceutical Sciences collection, Vol. 95, pp. 183-226 (H. Brittain ed., 1999)
Haleblian	John Haleblian & Walter McCrone, Pharmaceutical Applications of Polymorphism, *J. Pharm. Sci.* 58:911 (1969)
ICH 1994	ICH Harmonised Tripartite Guideline, Dose-Response Information to Support Drug Registration (Mar. 10, 1994)
ICH Guidelines	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (1999)
IMiDs	immunomodulatory drugs
JTX	Joint trial exhibit

Term	Definition
Kavanaugh 2014	Kavanaugh et al., "Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor," *Ann. Rheum. Dis.*, 73: 1020-26 (2014)
LPS	Lipopolysaccharide
Marriott 2001	Marriott et al., "Immunotherapeutic and antitumor potential of thalidomide analogues," *Expert Opinion on Biological Therapy*, 1(4): 675-82 (2001)
Muller 1998	Muller et al., "Thalidomide Analogs and PDE4 Inhibition," *Bioorganic & Medicinal Chemistry*, 8: 2669-74 (1998)
NCT '092	Clinical Trial No. NCT00456092, "A Phase II, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Efficacy and Safety Study of CC-10004 in Subjects with Active Psoriatic Arthritis"
NDA	New Drug Application
Papp 2012	Papp et al., "Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial," *Lancet*, 738-46 (2012)
PASI	Psoriasis Area and Severity Index
Pathan 2012	Pathan et al., "Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in ankylosing spondylitis," *Ann. Rheum. Dis.*, 0:1-6 (2012)
PBMC	Peripheral blood mononuclear cells
PDE	Phosphodiesterase enzyme
PDE IV or PDE4	Phosphodiesterase enzyme 4
PDX	Plaintiff's demonstratives
PTX	Plaintiff trial exhibit
POSA	Person of Ordinary Skill in the Art
Patent Office	U.S. Patent and Trademark Office
Sandoz	Sandoz Inc.

Term	Definition
Schett 2012	Schett et al., "Oral Apremilast in the Treatment of Active Psoriatic Arthritis," *Arthritis & Rheumatism*, 64(10): 3156-67 (2012)
SelCIDs	Selective cytokine inhibitory drugs
SOF	Stipulation of Facts
Suryanarayanan	Raj Suryanarayanan, *X-Ray Powder Diffractometry*, *in* Physical Characterization Of Pharmaceutical Solids (Harry G. Brittain ed., 1995)
Takeuchi	Takeuchi et al., "(R)- and (S)-3-Fluorothalidomides: Isosteric Analogues of Thalidomide," *Organic Letters*, 1(10), 1571-73 (1999)
TGA	Thermogravimetric analysis
TNFα or TNF-α	Tumor necrosis factor α
WO '606	WO 01/34606
WO '102	WO 2011/063102
Wu	Wu et al., "First-time-in-man, safety/tolerability and pharmacokinetics of ascending oral doses of apremilast (APR) in healthy subjects (HS), *Journal of Investigative Dermatology*, Vol. 131, No. 515 (2011)
XRPD	X-ray powder diffraction
Zydus	Zydus Pharmaceuticals (USA) Inc.

TABLE OF WITNESSES

Witness	Live or By Deposition	Description
Andrew Alexis, M.D., M.P.H.	Live	Dr. Alexis is Amgen's expert in the field of dermatology, including the treatment of dermatologic conditions such as psoriasis.
Stephen Davies, Ph.D., D.S.	Live	Dr. Davies is Amgen's expert in the field of synthetic, organic, and medicinal chemistry, including stereochemistry, and as well as in the synthesis and characterization of molecules and their use in pharmaceuticals.
Elaine S. Gilmore, MD, Ph.D.	Live	Dr. Gilmore is Defendants' expert in the field of dermatology, and specifically in the treatment of psoriasis.
Fabia Gozzo, Ph.D.	Live	Dr. Gozzo is Amgen's expert in the field of synchrotron radiation x-ray powder diffraction and structural characterization of materials.
Gordon W. Gribble, Ph.D.	Live	Dr. Gribble is Defendants' expert in the field of chemistry, organic chemistry, and medicinal chemistry, including stereochemistry and their use and development of pharmaceutical compositions.
Ivan T. Hofmann, C.P.A., C.F.F., C.L.P.	Live	Mr. Hoffmann is Defendants' expert in the field of pharmaceutical economics and market analysis, including economic issues involving intellectual property.
Susan Kim, Pharm.D.	By Deposition	Dr. Kim was Executive Director, U.S. Marketing at Amgen Inc. from November 2019 until her departure from Amgen in December 2020, and previously served in the same role at Celgene Corp. Dr. Kim was a Fed. R. Civ. P. 30(b)(6) corporate designee for Amgen.
Richard Knowles, Ph.D.	Live	Dr. Knowles is Amgen's expert in the field of biochemistry, pharmacology, and drug discovery, including in the field of PDE4 inhibitors.

Witness	Live or By Deposition	Description
Steven Miller, Ph.D.	Live	Dr. Miller is Zydus' expert in the field of characterization, identification and analysis of polymorphs.
George Muller, Ph.D.	By Deposition	Dr. Muller is a named inventor on the '536, '101, '283, and '638 patents.
Allan S. Myerson, Ph.D.	Live	Dr. Myerson is Amgen's expert in the field chemical engineering, the study of crystalline forms, and the pharmaceutical manufacturing, and industrial applications of crystallization in pharmaceutical formulations.
Clive Page, Ph.D.	Live	Dr. Page is Defendants' expert in the field of pharmacology and drug discovery, including in the field of PDE inhibitors and the treatment of inflammatory diseases.
Richard Person	By Deposition	Mr. Person is a Senior Commercial Counsel at Amgen and was a Fed. R. Civ. P. 30(b)(6) corporate designee for Amgen.
Patricia Rohane, Ph.D.	By Deposition	Dr. Rohane was Vice President, Clinical Research and Development, Immunology and Inflammation at Celgene Corp. from June 2003 until May 2010. Dr. Rohane is expected to testify about, among other things, Otezla®, its titration schedule, and its research and development, and clinical trials.
Mark J. Sacchetti, Ph.D.	Live	Dr. Sacchetti is Zydus' expert in the field of solid state chemistry, pharmaceutical science, polymorphism and polymorph screening.
Peter Schafer, Ph.D.	Live	Dr. Schafer is a named inventor on the '536, '101, '283, and '638 patents. Dr. Schafer was a Fed. R. Civ. P. 30(b)(6) corporate designee for Amgen.
Daniel O. Scharfstein, Sc.D.	Live	Dr. Scharfstein is Defendants' expert in the field of biostatistics.

Witness	Live or By Deposition	Description
William Smith, Esq.	Live	Mr. Smith is Amgen's expert in Patent Office policies, practices, and procedures.
Johnathan W. Steed, Ph.D.	Live	Prof. Steed is Defendants' expert in the field of chemistry and crystallography.
Christopher Vellturo, Ph.D.	Live	Dr. Vellturo is Amgen's expert in the field of microeconomics, survey design and implementation, and the evaluation of commercial performance of pharmaceutical products.
Jean Xu	By Deposition	Ms. Xu is a named inventor on the '101 and '283 patents.

I. Background

A. Parties

1. Plaintiff Amgen Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at One Amgen Center Drive, Thousand Oaks, California 91320. SOF ¶ 1.

2. Defendant Sandoz Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 100 College Road West, Princeton, New Jersey 08540. SOF ¶ 7.

3. Defendant Zydus Pharmaceuticals (USA) Inc. is a corporation organized and existing under the laws of the State of New Jersey, having a principal place of business at 73 Route 31 North, Pennington, New Jersey 08534. SOF ¶ 8.

4. Civil Action Nos. Nos. 18-11026 (consolidated), 18-11267, 18-11269, and 19-18806 have been consolidated for all purposes, including discovery, case management, and trial under the lead case docket number 18-11026 (hereinafter "Consolidated Actions"). SOF ¶ 9; Stipulation and Order (D.I. 424); Tr. 5:9-12.

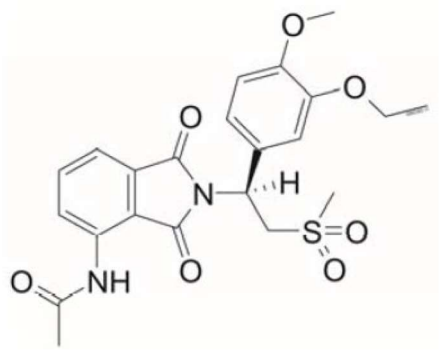
B. Amgen's NDA

5. According to the records of the FDA, Amgen holds approved New Drug Application ("NDA") No. 205437 for 10 mg, 20 mg, and 30 mg, oral apremilast tablets, which are sold in the United States under the trademark OTEZLA®. SOF ¶ 10.

6. Under the prescribing information approved as of 06/2020, OTEZLA® tablets are FDA-approved to treat adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy, adult patients with active psoriatic arthritis, and adult patients with oral ulcers associated with Behçet's Disease. *See* JTX-110 (OTEZLA® Prescribing Information, Revised 6/20). SOF ¶ 11.

7. The active ingredient in OTEZLA® is apremilast. SOF ¶ 12.

8. Apremilast can be represented by the chemical name, "(+)2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione," and the chemical structure shown below:



SOF ¶ 13.

9. Apremilast is a phosphodiesterase type 4 ("PDE4") inhibitor. SOF ¶ 14.

10. OTEZLA® is an embodiment of claims 3 and 6 of the '638 Patent. SOF ¶ 15.

11. The use of OTEZLA® according to the labeling for OTEZLA® is an embodiment of claim 6 of the '536 Patent. SOF ¶ 16.

12. The "Dosage and Administration" section of the labeling for OTEZLA® recites:

- To reduce the risk of gastrointestinal symptoms, titrate to recommended dose of 30 mg twice daily according to the following schedule (2.1)
    - Day 1: 10 mg in the morning
    - Day 2: 10 mg in the morning and 10 mg in the evening
    - Day 3: 10 mg in the morning and 20 mg in the evening
    - Day 4: 20 mg in the morning and 2o mg in the evening
    - Day 5: 20 mg in the morning and 30 mg in the evening
    - Day 6 and thereafter: 30 mg twice daily
- Dosage in Severe Renal Impairment:
    - Recommended dose is 30 mg once daily (2.2)

- For initial dosage titration, titrate using only morning schedule listed in Table 1 and skip afternoon doses (2.2)

SOF ¶ 17.

C. The Defendants' Abbreviated New Drug Applications

1. Sandoz's Proposed ANDA No. 211658

13. Sandoz submitted ANDA No. 211658 (the "Sandoz ANDA") to the FDA under 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, offer for sale, and/or sale of apremilast tablets ("Sandoz's ANDA Products"), a generic version of Amgen's OTEZLA® products. SOF ¶ 90.

14. The Sandoz ANDA references Amgen's NDA No. 205437. SOF ¶ 91.

15. Sandoz's ANDA included a Paragraph IV Certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) asserting that the '536 Patent, the '638 Patent, and the '101 Patent are invalid, unenforceable, or will not be infringed by the manufacture, use, offer for sale, sale and/or importation of Sandoz's ANDA Products. SOF ¶ 92.

16. Sandoz later amended its ANDA with a Patent Amendment as required under 21 CFR § 314.95(b) and 314.95(e) to include a new Paragraph IV Certification asserting that the '541 Patent is also invalid, unenforceable, or will not be infringed by the manufacture, use, offer for sale, sale and/or importation of Sandoz's ADNA Products. SOF ¶ 93.

2. Zydus's Proposed ANDA No. 211859

17. Zydus submitted ANDA No. 211859 (the "Zydus ANDA") to the FDA under 21 U.S.C. § 355 (j), seeking approval to engage in the commercial manufacture, use, offer for sale, sale and/or importation of apremilast tablets ("Zydus's ANDA Products"), a generic version of Amgen's OTEZLA® products. SOF ¶ 94.

18. The Zydus ANDA references Amgen's NDA No. 205437. SOF ¶ 95.

19. Zydus's ANDA included a Paragraph IV Certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) asserting that the '536 Patent, the '638 Patent, and the '101 Patent are invalid, unenforceable, or will not be infringed by the manufacture, use, offer for sale, sale and/or importation of Zydus's ANDA Products. SOF ¶ 96.

20. Zydus later amended its ANDA with a Patent Amendment as required under 21 CFR § 314.95(b) and 314.95(e) to include a new Paragraph IV Certification asserting that the '541 Patent is also invalid, unenforceable, or will not be infringed by the manufacture, use, offer for sale, sale and/or importation of Zydus's ADNA Products. SOF ¶ 97.

D. The Lawsuit

21. In May 2018, Defendants each submitted an ANDA with a Paragraph IV Certification seeking FDA approval for their ANDA. SOF ¶ 98.

22. Between June 26, 2018, and July 11, 2018, Celgene Corp. ("Celgene") filed suit against the Defendants alleging infringement of varying combinations of the '536 Patent, the '638 Patent, and the '101 Patent against each Defendant under 35 U.S.C. § 271(e)(2)(A). SOF ¶ 99.

23. Celgene also sought a declaratory judgment that defendants will, upon FDA-approval of Defendant's ANDA Product, directly infringe the '536 Patent, the '638 Patent, and the '101 Patent, will induce infringement of the '536 Patent, the '638 Patent, and the '101 Patent. Defendants counterclaimed seeking declaratory judgment of the noninfringement and invalidity of the '536 Patent, the '638 Patent, and the '101 Patent. SOF ¶ 100.

24. Between September 2018 and February 2019, Defendants each amended their ANDAs to include a Paragraph IV Certification with respect to the '541 Patent. SOF ¶ 101.

25. Celgene filed amended complaints alleging infringement of the '541 Patent against all Defendants under 35 U.S.C. § 271(e)(2)(A). Celgene also sought a declaratory

judgment that defendants will, upon FDA-approval of Defendant's ANDA Product, directly infringe the '541 Patent, will induce infringement of the '541 Patent, and will contribute to the infringement of the '541 Patent. Defendants counterclaimed seeking declaratory judgement of noninfringement and invalidity of the '541 Patent. SOF ¶ 102.

26. On October 22, 2018, the Court consolidated the cases against each respective Defendant into civil action 18-11026-MAS-DEA. SOF ¶ 103

27. On October 8, 2019, Celgene filed suit alleging infringement of the '283 Patent against Zydus (civil action (19-18806). SOF ¶ 104.

28. On December 19, 2019, the Court consolidated civil action 19-18806 against Zydus into the Consolidated Action. SOF ¶ 105.

29. On February 14, 2020, the Court granted Celgene and Amgen's motion to substitute Amgen for Celgene as Plaintiff in this action. SOF ¶ 106.

II. The Patents-In-Suit

A. The '638 Patent

30. United States Patent No. 7,427,638 ("the '638 Patent") is entitled "(+)-2-[1-(3-Ethoxy-4-Methoxyphenyl)-2-Methylsulfonylethyl]-4-Acetylaminoisoindoline-1,3-Dione, and Methods of Synthesis and Compositions Thereof." SOF ¶ 18; JTX-3.2.

31. The '638 Patent issued on September 23, 2008. SOF ¶ 19; JTX-3.2.

32. George W. Muller, Peter H. Schafer, Han-Wah Man, and Chuansheng Ge are the inventors named on the cover of the '638 Patent. SOF ¶ 20; JTX-3.2.

33. Celgene Corporation was listed as the assignee of the '638 Patent when it issued. JTX-3.2.

34. According to the records of the U.S. Patent and Trademark Office, Amgen is the current assignee of the '638 Patent. SOF ¶ 21.

35. The ’638 Patent issued from U.S. Patent Application. No. 11/106,142, filed on April 13, 2005. SOF ¶ 22; JTX-3.2.

36. Amgen is asserting Claims 3 and 6 of the ’638 Patent (the “’638 Patent Asserted Claims”) against all Defendants in this consolidated action. SOF ¶ 23.

37. The ’638 Patent is listed in the FDA’s Approved Drug Products with Therapeutic Evidence Equivalence Evaluations (the “Orange Book”) for OTEZLA® (NDA No. 205437). SOF ¶ 24.

38. The FDA’s Orange Book lists the expiration date of the ’638 Patent as February 16, 2028. SOF ¶ 25.

39. Claim 1 of the ’638 Patent is an independent claim and recites: “[a] pharmaceutical composition comprising stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or a pharmaceutically acceptable salt, solvate, or hydrate, thereof; and a pharmaceutically acceptable carrier, excipient or diluent.” SOF ¶ 26; JTX-3.23.

40. Claim 2 of the ’638 Patent recites: “[t]he pharmaceutical composition of claim 1 wherein said pharmaceutical composition is suitable for parenteral, transdermal, mucosal, nasal, buccal, sublingual, or oral administration to a patient.” SOF ¶ 27; JTX-3.23.

41. Claim 3 of the ’638 Patent recites: “[t]he pharmaceutical composition of claim 2 wherein said pharmaceutical composition is suitable for oral administration to a patient.” SOF ¶ 28; JTX-3.23.

42. Claim 4 of the ’638 Patent recites: “[t]he pharmaceutical composition of claim 2 wherein the amount of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-

methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is from 1 mg to 1000 mg." SOF ¶ 29; JTX-3.23.

43. Claim 5 of the '638 Patent recites: "[t]he pharmaceutical composition of claim 4 wherein the amount of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is from 5 mg to 500 mg." SOF ¶ 30; JTX-3.23.

44. Claim 6 of the '638 Patent recites: "[t]he pharmaceutical composition of claim 5 wherein the amount of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is from 10 mg to 200 mg." SOF ¶ 31; JTX-3.23.

45. According to the Court's adopted construction, "stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione," as it appears in claims 3 and 6 of the '638 Patent, means "a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound, wherein that one stereoisomer is (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione." *See* Claim Construction Order (D.I. 187) at 2; SOF ¶ 73; Gribble Tr. 588:25-589:19.

B. The '536 Patent

46. United States Patent No. 8,455,536 ("the '536 Patent") is entitled, "Methods of Using (+)-2-[1-(3-Ethoxy-4-Methoxyphenyl)-2-Methylsulfonylethyl]-4-Acetylaminoisoindoline-1,3-Dione." SOF ¶ 32; JTX-7.2.

47. The '536 Patent issued on June 4, 2013. SOF ¶ 33; JTX-7.2.

48. George W. Muller, Peter H. Schafer, Han-Wah Man, and Chuansheng Ge are the inventors named on the cover of the '536 Patent. SOF ¶ 34; JTX-7.2.

49. Celgene Corporation was listed as the assignee of the '536 Patent when it issued. JTX-7.2.

50. According to the records of the U.S. Patent and Trademark Office, Amgen is the current assignee of the '536 Patent. SOF ¶ 35.

51. The '536 Patent issued from U.S. Patent Application No. 12/630,788, filed on December 3, 2009. SOF ¶ 36; JTX-7.2.

52. The '536 patent's priority date is March 20, 2002. Alexis Tr. 1746:5-8; Gilmore Tr. 866:13-15.

53. Amgen is asserting Claim 6 of the '536 Patent (the "'536 Patent Asserted Claim") against all Defendants in this consolidated action. SOF ¶ 37.

54. The '536 Patent is listed in the FDA's Orange Book for OTEZLA® (NDA No. 205437). SOF ¶ 38.

55. The FDA's Orange Book lists the expiration date of the '536 Patent as March 19, 2023. SOF ¶ 39.

56. Claim 1 of the '536 Patent is an independent claim and recites: "[a] method of treating psoriasis, which comprises orally administering to a patient having psoriasis about 10 mg to about 200 mg per day of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, wherein the compound is administered in the form of a tablet or capsule as either a single dose or a divided dose." SOF ¶ 40; JTX-7.20-21.

57. Claim 6 of the '536 Patent recites: "[t]he method of claim 1, wherein the stereomerically pure compound comprises greater than about 97% by weight of (+) isomer based on the total weight percent of the compound." SOF ¶ 41; JTX-7.21.

58. According to the Court's adopted construction, "stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione," as it appears in claims 1 and 6 of the '536 Patent, means "a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound, wherein that one stereoisomer is (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione." *See* Claim Construction Order (D.I. 187) at 2; SOF ¶ 73; Gribble Tr. 588:25-589:19.

C. The '101 Patent

59. The '101 Patent is titled "Solid Forms Comprising (+)-2-[1-(3-Ethoxy-4-methoxypheny1)-2-methylsulfonylethy1]-4-acetylaminoisoindoline-1,3-dione, Compositions thereof, and Uses thereof." SOF ¶ 42; JTX-5.2; Steed Tr. 1081:16-20.

60. The '101 Patent generally relates to solid forms of apremilast, including apremilast crystalline Form B, compositions and uses thereof. Steed Tr. 1069:4-7.

61. Celgene Corporation was listed as the assignee of the '101 patent when it issued. JTX-5.2; Steed Tr. 1080:19-21.

62. According to the records of the U.S. Patent and Trademark Office, Amgen is the current assignee of the '101 Patent. SOF ¶ 45.

63. The '101 Patent lists George W. Muller, Peter H. Schafer, Hon-Wah Man, Chuansheng Ge, and Jean Xu as the named inventors. SOF ¶ 44; JTX-5.2.

64. The '101 Patent was filed on March 27, 2008, SOF ¶ 46, as a continuation-in-part ("CIP") application of earlier-filed, related applications. JTX-5.2; Steed Tr. 1080:22-1081:3; Myerson Tr. 1573:12-17.

65. The earliest filed related application is U.S. Provisional Application No. 60/366,515 ("the '515 application"), filed on March 20, 2002. JTX-5.2; Steed Tr. 1081:8-12.

66. A CIP application adds new information to the patent specification of earlier-filed, related applications. Steed Tr. 1081:3-7; Myerson Tr. 1573:12-17.

67. Celgene added new information to the '101 Patent specification for the first time on March 27, 2008, describing solid forms of apremilast, and methods for preparing and characterizing solid forms of apremilast. JTX-5.5-32 (newly added figures 1-28 disclosing results from analytical testing of apremilast crystalline forms A, B, C, D, E, F, and G, using four different solid form characterization techniques XRPD, DSC, TGA, and DVS); *see also* Steed Tr. 1082:4-24, 1077:15-1079:14; JTX-5.42-44 (10:39-13:5) (newly added definitions of terms and phrases associated with solid forms, crystalline and amorphous forms, and techniques for characterizing crystalline and amorphous forms); *see also* Steed Tr. 1084:1-14; JTX-5.46-51 (17:10-27:50) (newly added information to the "Detailed Description of the Invention" section of the '101 patent identifying seven apremilast crystalline forms A, B, C, D, E, F, and G, and methods for preparing and characterizing these solid forms of apremilast); *see also* Steed Tr. 1084:19-1085:11; JTX-5.62-66 (50:49-57:40) (newly added Example 12 describing apremilast solid form screening experiments that led to the identification of apremilast solid forms, including seven apremilast crystalline forms A, B, C, D, E, F, and G, and an amorphous form, methods for characterizing these solid forms of apremilast, and results from various studies performed on these apremilast solid forms); *see also* Steed Tr. 1088:11-1090:7.

68. Only after adding the above-described new information to the '101 Patent on March 27, 2008, Celgene sought and obtained claims to apremilast crystalline Form B. Steed Tr. 1090:8-14.

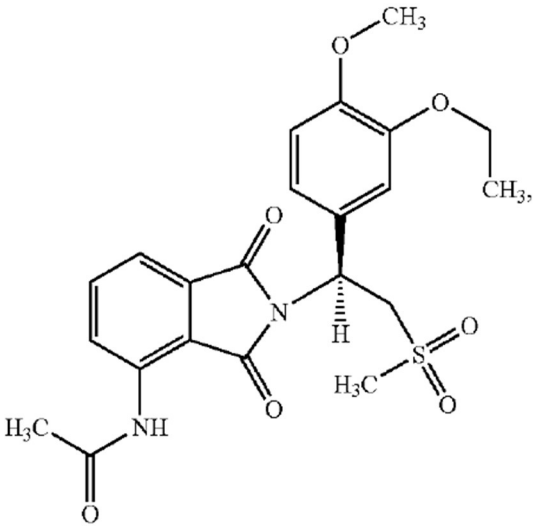
69. The '101 Patent is listed in the FDA's Orange Book for OTEZLA® (NDA No. 205437). SOF ¶ 48.

70. The FDA's Orange Book lists the expiration date of the '101 Patent as December 9, 2023. SOF ¶ 49.

71. Amgen is asserting Claims 1 and 15 of the '101 Patent (the "'101 Patent Asserted Claim") against all Defendants in this consolidated action. SOF ¶ 47.

72. Claim 1 of the '101 Patent is an independent claim and recites "[a] Form B crystal form of the compound of Formula (I):

(I)



which is enantiomerically pure, and which has an X-ray powder diffraction pattern comprising peaks at about 10.1, 13.5, 20.7, and 26.9 degrees 2θ." SOF ¶ 50; JTX-5.67.

73. Claim 15 of the '101 Patent recites "[a] solid pharmaceutical composition comprising the crystal form of any one of claims 1 and 2 to 13." SOF ¶ 51; JTX-5.67.

74. According to the Court's adopted construction, "enantiomerically pure," as it appears in claim 1 of the '101 Patent, means "a stereomerically pure composition of a compound having one chiral center." *See* Claim Construction Order (D.I. 187) at 2; SOF ¶ 73. Because apremilast has one chiral center, "enantiomerically pure" means "stereomerically pure," as it

appears in the asserted claims of the '638 Patent and the '536 Patent. Steed Tr. 1072:4-9; *see also* Gribble Tr. 588:25-589:19.

D. The '283 Patent

75. United States Patent No. 8,093,283 ("the '283 Patent") is entitled, "Solid Forms Comprising (+)-2-[1-(3-Ethoxy-4-Methoxyphenyl)-2-Methylsulfonylethyl]-4-Acetylaminoisoindoline-1,3-Dione, Compositions Thereof, and Uses Thereof." JTX-6.2; SOF ¶ 52.

76. The '283 Patent issued on January 10, 2012. JTX-6.2; SOF ¶ 53.

77. George W. Muller, Peter H. Schafer, Hon-Wan Man, Chuansheng Ge, and Jean Xu are the inventors named on the cover of the '283 Patent. JTX-6.2; SOF ¶ 54.

78. Celgene Corporation was listed as the assignee of the '283 Patent when it issued. JTX-6.2.

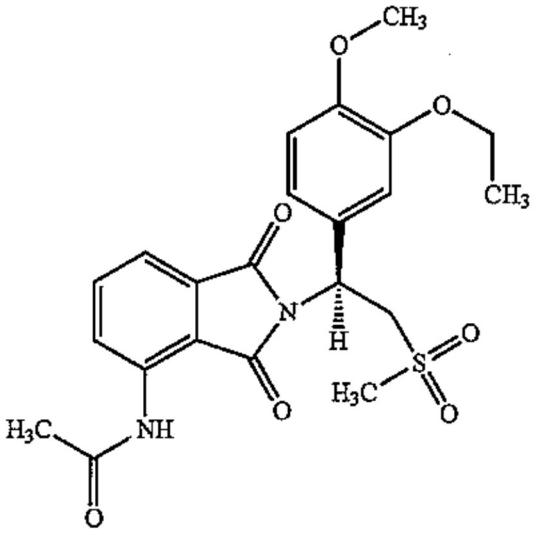
79. According to the records of the U.S. Patent and Trademark Office, Amgen is the current assignee of the '283 Patent. SOF ¶ 55.

80. The '283 Patent issued from U.S. Patent Application No. 12/945,800, filed on November 12, 2010. JTX-6.2; SOF ¶ 56.

81. Amgen is asserting Claims 2 and 27 of the '283 Patent (the "'283 Patent Asserted Claims") against Zydus in this consolidated action. SOF ¶ 57.

82. The FDA's Orange Book lists the expiration date of the '283 Patent as March 19, 2023. SOF ¶ 58.

83. Claim 1 of the '283 Patent is an independent claim and recites: "[a]n unsolvated crystal form of the compound of Formula (I):



which is enantiomerically pure, wherein the crystal form is Form A, which has an X-ray powder diffraction pattern comprising peaks at 8.1, 14.4, 17.4, 23.6 and 25.1 degrees 2θ, or Form F, which has an X-ray powder diffraction pattern comprising peaks at about 8.1, 15.6, 17.3, and 25.4 degrees 2θ." JTX-6.66; SOF ¶ 59.

84. Claim 2 of the '283 Patent recites: "[t]he crystal form of claim 1, wherein the crystal form is Form A, which has an X-ray powder diffraction pattern comprising peaks at about 8.1, 14.4, 17.4, 23.6, and 25.1 degrees 2θ." JTX-6.66; SOF ¶ 60.

85. Claim 27 of the '283 Patent is an independent claim and recites: "[a] solid pharmaceutical composition comprising the crystal form of claim 2." JTX-6.66; SOF ¶ 61.

86. According to the Court's adopted construction, "enantiomerically pure," as it appears in claim 1 of the '283 Patent, means "a stereomerically pure composition of a compound having one chiral center." *See* Claim Construction Order (D.I. 187) at 2; SOF ¶ 73. Because apremilast has one chiral center, "enantiomerically pure" means "stereomerically pure," as it appears in the asserted claims of the '638 Patent and the '536 Patent. Sacchetti Tr. 1173:20-1174:7; *see also* Gribble Tr. 588:25-589:19.

E. The '541 Patent

87. The '541 Patent is entitled, "Methods for the Treatment of Diseases Ameliorated by PDE4 Inhibition Using Dosage Titration of Apremilast." JTX-13.2; SOF ¶ 62.

88. The '541 Patent generally relates to a method of treating patients with psoriasis by administering apremilast according to a six-day dosing titration schedule, ranging from a 10 mg to 60 mg daily dose. Gilmore Tr. at 830:18-24.

89. Celgene Corporation was listed as the assignee of the '541 Patent when it issued. JTX-13.2; Gilmore Tr. 829:8-11.

90. According to the records of the U.S. Patent and Trademark Office, Amgen is the current assignee of the '541 Patent. Gilmore Tr. 829:12-13; SOF ¶ 65.

91. The '541 Patent lists Robert Day as the named inventor. JTX-13.2; Gilmore Tr. 829:8-11; Alexis Tr. 1803:19-21.

92. The '541 Patent issued from U.S. Patent Application No. 14/826,027, filed on August 13, 2015. SOF ¶ 66.

93. The effective filing date of the '541 Patent is August 15, 2014, the filing date of U.S. Provisional Application No. 62/038,176. SOF ¶ 66; JTX-13.2; Gilmore Tr. 829:18-21; Alexis Tr. 1752:20-23, 1804:7-20.

94. Amgen is asserting Claims 2, 19, and 21 of the '541 Patent (the "'541 Patent Asserted Claim") against all Defendants in this consolidated action. SOF ¶ 67.

95. The '541 Patent is listed in the FDA's Approved Drug Products with Therapeutic Evidence Equivalence Evaluations (the "Orange Book") for OTEZLA® (NDA No. 205437). SOF ¶ 68.

96. The FDA's Orange Book lists the expiration date of the '541 Patent as May 29, 2034. SOF ¶ 69.

97. Claim 2 of the '541 Patent is an independent claim and recites: "[a] method for treating a patient with stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, wherein the patient is suffering from psoriasis, the method consisting of: (a) administering to the patient stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione in an initial titration dosing schedule consisting of (i) 10 mg in the morning on the first day of administration; (ii) 10 mg in the morning and 10 mg after noon on the second day of administration; (iii) 10 mg in the morning and 20 mg after noon on the third day of administration; (iv) 20 mg in the morning and 20 mg after noon on the fourth day of administration; (v) 20 mg in the morning and 30 mg after noon on the fifth day of administration; and (b) on the sixth and every subsequent day, administering to the patient 30 mg in the morning and 30 mg after noon of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione." JTX-13.20 (31:3-26); SOF ¶ 70.

98. Claim 19 of the '541 Patent recites: "[a] method as in any one of claims 1-14, wherein the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione comprises greater than about 98% by weight of the (+) isomer of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione based on the total weight percent of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione." JTX-13.22 (36:22-29); SOF ¶ 71.

99. Claim 21 of the '541 Patent recites: "[a] method as in any one of claims 1-14, wherein the stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is administered in tablet form." JTX-13.22 (36:38-41); SOF ¶ 72.

100. As acknowledged by Amgen's expert Dr. Alexis, claim 2 only recites a method of treating psoriasis, and does not contain any element requiring a reduction in adverse events. Alexis Tr. 1805:5-15 ("Q . . . Claim 2 does not contain any element that requires this method of treating psoriasis to reduce adverse events, does it? A. What claim 2 describes is a method for treating the patient with the compound apremilast, wherein the patient is suffering from psoriasis . . . Q. And it doesn't say anything about reducing adverse events in this claim, does it? A. it only speaks to the method").

101. The only allegedly inventive feature of the asserted claims of the '541 patent is the specific dosing titration schedule. The named inventor did not invent the compound apremilast. Alexis Tr. 1811:1-3. The named inventor did not invent the use of apremilast to treat psoriasis. Alexis Tr. 1811:4-6. The named inventor did not invent administering 30 mg of apremilast twice per day to treat psoriasis. Alexis Tr. 1811:7-13.

III. Scope And Content Of The Prior Art For The '638 and '536 Patents.

A. Stereochemistry and Enantiomers

200. Compounds that have no plane of symmetry are termed "chiral" or "asymmetric" and are not superimposable on their mirror image. The most common chiral compound is one with a "chiral carbon," also called a "chirality center," "chirality carbon," "asymmetric center", or "asymmetric carbon." (Gribble Tr. 576:13-577:13; DDX2-12; JTX-133.6-7)

201. When a carbon atom in an organic molecule contains four bonds, and four different atoms, or groups of atoms, are attached to that carbon through those bonds, there are two different ways that those four atoms or groups can be arranged. The central carbon atom is referred to as a chiral center or asymmetric carbon. (Gribble Tr. 576:13-577:13; Davies Tr. 89:4-6; JTX-133.6-7; DDX2-13.)

202. Examples of chiral compounds are enantiomers. Enantiomers are pairs of stereoisomers that are non-superimposable mirror images of each other. One can identify structures that can exist as enantiomers by learning to recognize chiral carbons within a chemical formula. (Gribble Tr. 576:13-578:11; DDX2-13; JTX-133.6-7.)

203. Stereochemistry is the examination of the three-dimensional nature of molecules, or how atoms in a molecule are arranged in space relative to one another. (Gribble Tr. 579:14-23; Davies Tr. 83:15-17; DDX2-13.)

204. Enantiomers have the same molecular formula and atoms connected in the same sequence but have different three-dimensional arrangements. (Gribble Tr. 578:20-579:4; DDX2-13.)

205. The only difference between enantiomers is the orientation of the atoms in space. (Davies Tr. 1448:4-8; DDX-119.1.)

206. Enantiomers have the same physical and chemical properties (such as solubility and melting point), except for the direction in which they rotate a plane of polarized light. This is why enantiomers are sometimes referred to as optical isomers. (Gribble Tr. 577:16-578:19; JTX-133.12-15; DDX2-13.)

207. Enantiomers and the racemate have the same chemical formula and same chemical structure. (Gribble Tr. 579:5-13.)

208. In a racemate, one enantiomer is in S-configuration and the other enantiomer is in the R-configuration. (Davies Tr. 1405:11-13.)

209. A racemic compound is a mixture of equal parts of enantiomers that is an equimolar mixture of two enantiomers such that the optical rotation is zero. (Gribble Tr. 580:1-6; Davies Tr. 94:12-14; DDX2-14; JTX-133.20; JTX-134.1.)

210. In a racemic mixture, the optical rotation of one enantiomer exactly cancels the optical rotation of the other enantiomer. (Gribble Tr. 580:1-6.)

211. A racemic compound is also called a "racemate." A racemic mixture may be represented by "(±)" (Gribble Tr. 580:1-6; DDX2-14; JTX-133.20.)

212. A chemist looking at the name of a compound would understand that if there is no (+) or (-) symbol before the name, they would assume that it is a racemate. (Davies Tr. 96:14-25.)

213. Optical rotation refers to the rotation of plane-polarized light as measured in a polarimeter for a chiral molecule. (Gribble Tr. 578:12-19; DDX2-13.)

214. Because all of the physical and chemical properties of a pair of enantiomers are the same, each enantiomer will demonstrate different interactions with other chiral substances and different interactions with polarized light. (Gribble Tr. 577:16-578:11, 580:9-581:3; DDX2-13, 14; JTX-133.23-25.)

215. When plane-polarized light is passed through a solution containing a single enantiomer, the plane of polarized light is rotated either to the right/clockwise, which is represented by "(+)", or to the left/counterclockwise, which is represented by "(-)." (Gribble Tr. 578:12-19; DDX2-13; JTX-133.12-13.)

216. Optical and stereomeric purity refer to the same thing. Optical and stereomeric purity refer to a mixture of enantiomers where one enantiomer is enriched over the other. (Gribble Tr. 595:3-7; Davies Tr. 1406:3-11.)

217. Each pair of enantiomers are also assigned an "(R)" and "(S)" nomenclature. The direction of optical rotation is not related to the (R) and (S) nomenclature. The system of (R) and

(S) nomenclature for chiral molecules is used to indicate the absolute configuration of groups around a chiral carbon. (JTX-133.13-14.)

218. There are several reasons why one would want to use a single enantiomer in a pharmaceutical drug substance. (Gribble Tr. 581:21-582:10; DDX2-15, 16; JTX-133.23-25; JTX-181.5; DTX-118; DTX-119.)

219. One enantiomer may be more active than the other, one enantiomer may be totally inactive and the other is active, the two enantiomers may have identical activities, the enantiomers may have different (but not harmful) activities, or one enantiomer may be harmful and the other enantiomer is not. (Gribble Tr. 580:9-581:19; DDX2-15; JTX-133.23-25.)

220. Biological processes are highly stereospecific and in nature, chiral, optically-pure or stereomerically-pure molecules are very common. (Gribble Tr. 581:4-18; DDX2-15; JTX-133.23-25.)

221. The stereochemistry of a compound can affect its binding affinity and fit within a biological receptor. Because enzymes themselves are chiral, enzymes can be enantiomerically-selective in their catalytic action. (Gribble Tr. 580:9-581:3; DDX2-15; JTX-133.23-25.)

222. Determining which enantiomer of a racemate, if any, demonstrates more or different pharmacological activity is a routine part of pharmaceutical drug development. The production of pure enantiomers of drugs is important in the pharmaceutical industry. (Gribble Tr. 581:22-582:14; DDX2-16; JTX-181.5.)

223. The Food and Drug Administration (FDA) has issued guidance and policy documents to address development of racemates, stereoisomers, and adequate pharmacological and toxicological assessments. (Gribble Tr. 581:21-582:14; DDX2-16; DTX-118.2; DTX-119.2.)

224. FDA's policy is that the properties of each individual enantiomer must be known before approving a drug for human use. (Gribble Tr. 581:21-582:14; DDX2-16; DTX-118.2; DTX-119.2.)

225. FDA has issued guidance and policy documents regarding racemates and stereoisomers because it is well known that one member of an enantiomeric pair may be inactive and the other active, but it is also possible that one member of an enantiomeric pair results in unacceptable toxicity and the other member is active without toxicity concerns. (Gribble Tr. 581:21-582:14; DDX2-16; DTX-118.2; DTX-119.2.)

226. "Now that technical advances (large scale chiral separation procedures or asymmetric synthesis) permit production of many single enantiomers on a commercial scale, it is appropriate to consider what FDA's policy with respect to stereoisomeric mixtures should be. Development of racemates raises issues of acceptable manufacturing control of synthesis and impurities, adequate pharmacologic and toxicologic assessment, proper characterization of metabolism and distribution, and appropriate clinical evaluation." (Davies Tr. 1446:12-1447:12; DDX-119.1.)

227. "The stereoisomeric composition of a drug with a chiral center should be known and the quantitative isomeric composition of the material used in the pharmacologic, toxicologic, and clinical studies known. Specifications for the final product should assure identify; strength, quality, and purity from a stereochemical viewpoint." (Davies Tr. 1448:9-1449:10; DDX-119.2.)

228. The pharmaceutical industry develops pure enantiomeric drugs for several reasons, including because the dose of a single enantiomer compared to the racemate would be only one-half for the patient, administration of a single enantiomer avoids possible side effects

from the other enantiomer, and preparation of single enantiomers avoids wasteful production of the unwanted enantiomer. (JTX-181.5.)

229. Long before March 2002, it was known in the art that pharmaceutical compounds that exist in more than one enantiomeric form should be tested to determine the relative activity of each enantiomer, and where there was a substantial difference in the pharmacological activity between the isomers, the introduction of a single enantiomer should be favored over the racemate. (Gribble Tr. 581:21-582:14; DDX2-16; DTX-118.2; DTX-119.2; DTX-133.23-25.)

230. In 1987, FDA published guidelines for submitting supporting documentation in drug applications for the manufacture of drug substances directed at the concern that enantiomers of chiral compounds can exhibit different pharmacological activities. (Gribble Tr. 581:21-582:14; DDX2-16; DTX-118.2.)

231. FDA Guidelines 1987 states that when a new drug substance (NDS) is asymmetric, "the sponsor should ideally (and prior to the submission of an IND) have either separated the various potential stereoisomers of the NDS or synthesized them independently…Individual stereoisomers may need to be studied for pharmacological and toxicological properties (and/or for safety and efficacy)." (Gribble Tr. 581:21-582:14; DDX2-16; DTX-119.2.)

232. It was well known in the art before 2002 that chirality is "important because for the majority of chiral drugs only one drug enantiomer has significant pharmacological activity," and "[t]he potential advantages of using pure enantiomeric drugs are a less complex and more selective pharmacological profile, a greater therapeutic index, less complex pharmacokinetics, less complex drug interactions and less complex plasma concentration-response relationships." (Gribble Tr. 580:9-581:19; DDX2-15; DDX2-16; JTX-134.1.)

233. Before 2002, the FDA had a policy in place stating that "[i]n general, it is more important to evaluate both enantiomers clinically and consider developing only one when both enantiomers are pharmacologically active but differ significantly in potency, specificity, or maximum effect…" (Gribble Tr. 581:22-582:11; DDX2-16; DTX-118.3; DTX-119)

234. The FDA warned that stereoisomers "are often readily distinguished by biological systems … and may have different pharmacokinetic properties (absorption, distribution, biotransformation, and excretion) and quantitatively or qualitatively different pharmacologic or toxicologic effects." (DDX2-16; DTX-118.1; DTX-119)

235. The FDA further stated that "*in vivo* measurement of individual enantiomers should be available to help assess toxicologic findings… Unless it proves particularly difficult, the main pharmacologic activities of the isomers should be compared in *in vitro* systems, in animals and/or in humans." (DDX2-16; DTX-118.2; DTX-119)

236. FDA Policy emphasized the importance of testing each stereoisomer separately, and it was well understood that this policy is intended to minimize unfavorable side effects or toxicity that can result from ingesting a racemic mixture in which one member of the enantiomeric pair has unwanted or adverse effects. (Gribble Tr. 581:22-582:11; DDX2-16; DTX-118.1-3; DTX-119.)

237. FDA considers enantiomers and racemates to be different entities, but the racemate is an entity comprised of the two enantiomers, so one-half of the racemate is identical to a single enantiomer of the racemate. (Gribble Tr. 642:14-24.)

238. A chemical entity is a combination of two enantiomers. (Gribble Tr. 642:25-643:4.)

B. Separating a Racemic Mixture into the Two Enantiomers

239. Stereoisomers will interact with other chiral compounds differently because of the particular spatial arrangement of groups within each stereoisomer. (Gribble Tr. 584:20-585:17.)

240. Resolution of a racemic mixture is the chemical or physical process of separating a racemic mixture into the two enantiomers. Resolution can be done by crystalline salt separation using tweezers; biological separation using metabolism of a microbe, fungus, or bacterium; diastereomeric salt separation; and chiral chromatography. (Gribble Tr. 582:17-584:14; DDX2-17; JTX133.20-22; JTX181.5-12; JTX-183.12-19.)

241. General techniques known in the art before filing of the '358 patent include chiral synthesis starting with an optically active starting material, chiral chromatography, salt resolution with a chiral acid. (Gribble Tr. 622:7-23.)

242. Racemates can be resolved into the individual enantiomers by crystallization such that one enantiomer crystallizes in one kind of asymmetric crystal configuration, and the other enantiomer crystallizes into another. Pasteur performed the first resolution of this sort in 1848 in a separation of the (+) and (–) forms of sodium ammonium tartrate. (Gribble Tr. 582:17-584:14; DDX2-17; JTX133.20-22; JTX181.5-12; JTX-183.12-19.)

243. Racemates can be resolved biologically. Enzyme systems (either inside or outside an organism) are allowed to consume or chemically modify one enantiomer and the other enantiomer is rejected. (Gribble Tr. 582:17-584:14; DDX2-17; JTX133.20-22; JTX181.5-12; JTX-183.12-19.)

244. Racemates can be resolved by diastereomeric salt formation. This is a chemical resolution uses an acid-base reaction between a racemic mixture of chiral carboxylic acids and an amine. This reaction results in each isomer forming different diastereomers that can then be separated by crystallization or some other means because the diastereomers are now different

compounds with different chemical and physical properties. (Gribble Tr. 582:17-584:14; DDX2-17; JTX133.20-22; JTX181.5-12; JTX-183.12-19.)

C. Chiral Chromatography

245. Column chromatography is a purification technique commonly used in organic synthesis and is the most efficient. (Gribble Tr. 582:17-584:14; DDX2-17; JTX133.20-22; JTX181.5-12; JTX-183.12-19.)

246. Column chromatography is based on the phenomenon that when a solution of a mixture of organic compounds is loaded onto a packed column with a substrate, different compounds interact differently with the substrate and the solvent and therefore they pass through the column at different rates, which result in the separation of the individual compounds. (Gribble Tr. 584:15-585:17; DDX2-18; JTX-183.12-19.)

247. Chromatography uses a column of support particles or beads to separate desired components that are dissolved in a solution. The support particles are often referred to as the column matrix or the stationary phase. A solvent system (also referred to as mobile phase or eluent) is used to move the desired component molecules along the column bed at varying rates, and various solvent mixtures and/or buffers can be used that allow for the desired molecules to associate with the stationary phase to a greater of lesser degree based on their differing chemical properties. (Gribble Tr. 584:15-585:17; DDX2-18; JTX-183.12-19.)

248. Chiral chromatography methods allow for separation, detection, and quantification of two enantiomers within a sample. A pair of enantiomers have the same chemical properties except for their interactions with other chiral substances, and therefore the enantiomers elute at different time points. (Gribble Tr. 584:15-585:17, 644:5-10; DDX2-18; JTX-183.12-19.)

249. In chiral chromatography, a chiral moiety or a chiral group or molecule is attached to the surface of the particles or beads, creating a chiral surface that can interact with the racemic sample that can be loaded onto the column for separation. Since each enantiomer will interact differently with a chiral stationary phase, one enantiomer will elute from the column more quickly than the other enantiomer, leading to fractions of the eluent that contain an enriched or fully resolved enantiomer, and other fractions that contain the other enantiomer in enriched or fully-resolved form. When the elution is complete, the resolved enantiomers would then be characterized, such as by analysis by optical rotation, to determine in which order the enantiomers were eluted. (Gribble Tr. 584:15-585:17; DDX2-18; JTX-183.12-19.)

250. Chiral chromatography is the best and most efficient method for separating enantiomers of a racemic mixture. (Gribble Tr. 586:7-12.)

251. Chiral chromatography can be performed on a large or small scale. (Gribble Tr. 586:7-12.)

252. Chiral chromatography is a mechanical separation technique; there is no chemical modification that occurs with the racemate or either enantiomer. Chiral chromatography takes advantage of the selective interaction of enantiomers with a chiral adsorbent in the column. (Gribble Tr. 585:18-24.)

D. Thalidomide And Its Analogues

253. Thalidomide was a known immunomodulatory drug and inhibitor of TNF-α. (JTX-66.1-4; JTX-68.1; JTX-239.2-4.)

254. Thalidomide was a known to have a range of immunological properties and initially marketed as a sedative. (JTX-66.1-4; JTX-68.1; JTX-239.2-4.)

255. Thalidomide became infamous after being withdrawn from the market due to its teratogenic properties. (JTX-66.2; JTX-68.1; JTX-239.2-4.)

256. Novel compounds were designed using thalidomide's structure as a lead to optimize its immunological and anticancer properties while decreasing its side effects. (JTX-66.2, 66.4.)

257. Thalidomide analogues can be grouped into at least two distinct classes: selective cytokine inhibitory drugs ("SelCID"), i.e., PDE4 inhibitors, and immunomodulatory drugs ("IMiD"), which do not inhibit PDE4 and have an unknown mechanism of action. (JTX-66.4.)

258. Both SelCIDs and IMiDs "are potent TNF-α inhibitors." (JTX-66.4.)

259. It was known that thalidomide analogues are potent inhibitors of PDE4. (JTX-69.5.)

260. By 2002, thalidomide analogues were being characterized in laboratory studies, and were assessed in Phase I and Phase I/II clinical studies for safety and efficacy in Crohn's disease. (JTX-66.6.)

261. The Phase I and Phase I/II clinical studies of thalidomide analogs were "encouraging," and provided an "exciting prospect" for the potential clinical efficacy of thalidomide analogues in a wide range of conditions, including conditions that could be ameliorated by PDE4 (and TNFα) inhibition, such as psoriasis. (JTX-66.7.)

262. Thalidomide is an example of a racemic drug where one isomer is less therapeutically active but is responsible for toxicity. However, separation of the (R) and (S) isomers did not achieve a separation of efficacy and toxicity due to racemization in vivo at the labile hydrogen. (JTX-239.1.)

263. Racemization refers to the interconversion between enantiomers. (JTX-239.1)

264. Despite the issues of toxicity with thalidomide, research continued on the compound and expanded to thalidomide analogues to seek compounds with similar

immunological properties but without the serious risk of teratogenicity. (Gribble Tr. 613:12-23; DDX2-53; JTX-66; JTX-68; JTX-69; JTX-239.)

265. The investigation of thalidomide analogues led to the identification of two categories of selective cytokine inhibitory drugs, one of which ("SelCID") was known to inhibit PDE4. (JTX-66.)

266. Thalidomide analogues were synthesized or separated as pure enantiomers and assessed for the ability to inhibit release TNF-α using common assays, such as LPS-stimulated PBMCs (peripheral blood mononuclear cells). (JTX-239.)

267. Formula I in the '358 patent does not cover thalidomide and thalidomide is not mentioned in the '358 patent. (Gribble Tr. 19-23; Davies Tr. 1420:3-10; DDX2-43; DTX-174.4-6.)

E. Pharmaceutical Formulations

268. A pharmaceutical formulation is a combination of a drug substance with inactive carriers or excipients. There are many reasons that drugs are almost always given in formulated preparations, including flavor, compression, and stability. (Gribble Tr. 586:22-587.6; DDX2-19; JTX-135.8.)

269. Oral dosage forms are generally preferred because they are more convenient for the patient and result in better patient compliance with the prescribed dosing regimen. Oral delivery systems are also preferred for drugs requiring systemic administration. (Gribble Tr. 586:22-587.6; DDX2-19; JTX-135.8.)

F. Claim Construction

270. In the context of the construed claim terms, stereomerically pure apremilast means apremilast, the (+) isomer, substantially free of the (-) isomer. (Gribble Tr. 589:22-590:7 DDX2-23; DDX2-24.)

G. The '358 Patent

271. U.S. Patent No. 6,020,358, "Substituted Phenethylsulfones and Method of Reducing TNFα Levels," issued on February 1, 2000 to named inventors George W. Muller and Han Wah Man ("the '358 patent"). (Gribble Tr. 590:20-24; DDX2-26; DTX-174.1.)

272. The '358 patent issued before the earliest effective filing date of the '638 and '536 patents. (Gribble Tr. 590:25-591:3; DDX2-26; DTX-174.1; JTX-3.1; JTX-7.1.)

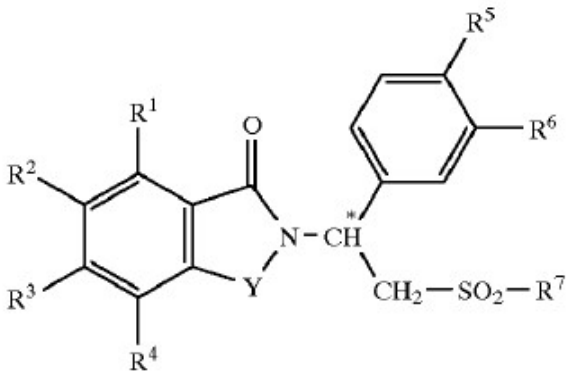
273. The '358 patent discloses substituted phenylethylsulfones as racemic mixtures according to a Formula I, and their use in inhibiting phosphodiesterases, particularly PDE IV (also referred to as PDE4), in the treatment of diseases mediated by inhibition of PDE IV, and included in exemplary oral formulations containing from 1 to 100 mg of Formula I compounds. (Gribble Tr. 591:6-15, 598:15-20; DTX-174 (4:66-6:18, 7:1-13, 9:22-24, 10:1-19:55.)

274. The '358 patent discloses that "[d]ecreasing TNFα levels, increasing cAMP levels, and inhibiting PDE IV thus constitute valuable therapeutic strategies for the treatment of many inflammatory, infectious, immunological or malignant diseases," including psoriasis and rheumatoid arthritis. (DTX-174.4 (4:35-49.))

275. The '358 patent also discloses that TNFα "plays a role in the area of chronic pulmonary inflammatory diseases," and that "compounds that inhibit PDE IV specifically, would exhibit the desirable inhibition of inflammation and relaxation of airway smooth muscle with a minimum of unwanted side effects, such as cardiovascular or anti-platelet effects." (DTX-174.4 (4:23-27).)

276. The '358 patent states that "the present invention is based on the discovery that certain classes of non-polypeptide compounds more fully described herein decrease the levels of TNFα." (DTX-174.4 (4:61-63).)

277. The phenylethylsulfone compounds of the '358 patent are disclosed by Formula I of the '358 patent:



(Gribble Tr. 591:6-15; DTX-174 (4:66–6-67).)

278. The '358 patent discloses that "the carbon atom designated * constitutes a center of chirality;" Y can be C=O; R^1, R^2, and R^3 can each be a hydrogen; R^4 can be $–NR^8R^9$ where each of R^8 and R^9, taken independently of the other, can be a hydrogen and the other is $–COR^{10}$ where R^{10} is an alkyl of 1 to 8 carbons; R^5 and R^6, independently of the other, can be an alkoxy of 1 to 4 carbon atoms; and R^7 can be an alkyl of 1 to 8 carbons. (DTX-174 (20:60–61 (claim 1).)

279. The '358 patent states:

> The compounds of Formula I possess a center of chirality and can exist as optical isomers. Both the racemates of these isomers and the individual isomers themselves, as well as diastereomers when there are two chiral centers, are within the scope of the present invention. The racemates can be used as such or can be separated into their individual isomers mechanically as by chromatography using a chiral absorbant. Alternatively, the individual isomers can be prepared in chiral form or separated chemically from a mixture by forming salts with a chiral acid, such as the individual enantiomers of 10-camphorsulfonic acid, amphoric acid, α-bromocamphoric acid, methoxyacetic acid, tartaric acid, diacetyltartaric acid, malic acid, pyrrolidone-5-carboxylic acid, and the like, and then freeing on or both of the resolved bases, optionally repeating the process, so as to obtain either or both substantially free of the other; i.e., in a form having an optical purity of >95%.

(DTX-174 (8:63–9:12).)

280. The inventors of the ’358 patent stated that enantiomers are within the scope of that invention. (Davies Tr. 1408:4-7; DTX-174 (8:63–9:12).)

281. The inventors of the ’358 patent stated that the racemates of that invention can be separated into the individual enantiomers. (Davies Tr. 1408:8-20; DTX-174 (8:63–9:12).)

282. The inventors of the ’358 patent disclosed methods to separate the racemates of that invention into the individual enantiomers. (Davies Tr. 1409:5-11; DTX-174 (8:63–9:12).)

283. The methods to separate the racemic compounds of the ’358 patent are taught at the university level. (Davies Tr. 1411:12-23.)

284. There are 26 Examples in the ’358 patent. (DTX-174 (10:1-20:13).)

285. Examples 1-20 name and provide methods of preparing specific compounds of Formula I (Examples 3-17 and 19-20) or name and provide methods of preparing starting materials to prepare specific compounds of Formula I (Examples 1, 2, and 18). Examples 21-26 describe formulations for exemplary compounds of Formula I, including tablets having 10 mg of a compound of Formula I (Example 24). (DTX-174 (10:1-20:13).)

286. The ’358 patent lists 20 examples of specific racemic compounds, 17 of which are final products of formula I. (Gribble Tr. 623:25-624:9.)

287. Out of the billions of compounds covered by Formula I, the inventors of the ’358 patent called out 17 specific, typical examples, which is an exceedingly small percentage of the total possible compounds. (Davies Tr. 1413:24-1414:22.)

288. In Example 12, the ’358 patent specifically names 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetamidoisoindoline-1,3-dione as a compound of Formula I, and a method of preparing it. (Gribble Tr. 591:18-592:7; DDX2-28; DTX-174 (14:34–55.)

289. Example 12 of the ’358 patent states that 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetamidoisoindoline-1,3-dione was prepared according to the procedure of Example 8 in the ’358 patent using 1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethylamine and 3-acetamidophthalic anhydride. (Gribble Tr. 592:8-593:1; DDX2-28; DTX-174 (14:40–45).)

290. The ’358 patent further discloses oral dosage forms, including tablets and capsules, containing from 1 to 100 mg of drug per unit of dosage form. (Gribble Tr. 598:4-12; DDX2-32; DTX-174 (9:22–43).)

291. The ’358 patent discloses that the compositions can be formulated into:

> physically discrete units suitable as a unitary dosage, or a predetermined fraction of a unitary dose to be administered in a single or multiple dosage regimen to human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with a suitable pharmaceutical excipient.

(DTX-174 (9:22–60).)

292. The ’358 patent further discloses that compounds of Formula I can be prepared as salts. (DTX-174 (9:13-21).)

293. The ’358 patent also states that “[p]harmaceutical compositions thus comprise one or more compounds of the present invention associated with at least one pharmaceutically acceptable carrier, diluent or excipient.” (Gribble Tr. 598:4-12; DDX2-32; DTX-174 (9:31–34).)

294. Claim 1 of the ’358 patent is directed to a genus of the compounds of Formula I and expressly identifies the chiral carbon in Formula I. (Gribble Tr. 598:23-599:5; DDX2-24; DTX-174 (20:15-29).)

295. Claim 17 of the ’358 patent is directed to reducing unacceptable levels of TNFα by administering a compound of claim 1. (DTX-174 (22:30-32).)

296. Claim 18 of the ’358 patent is directed to inhibiting PDE IV by administering a compound of claim 1. (Gribble Tr. 598:23-599:5; DDX2-24; DTX-174 (22:33-35).)

297. Claim 19 of the ’358 patent is directed to pharmaceutical compositions comprising a compound of claim 1 and a carrier, the amount of the compound of claim 1 being sufficient to reduce TNFα levels upon administration to a mammal. (DTX-174 (22:36-39).)

298. Formula I compounds in the ’358 patent are racemates, which a POSA would understand are made up of two enantiomers in a 1:1 mixture. (Davies Tr. 1400:4-20.)

299. In 2015, the Orange Book listed the ’358 patent as covering the apremilast compound. (Davies Tr. 1480:4-17; DTX-384.1000, 1277.)

IV. The Asserted Claims Of The ’638 Patent Are Invalid.

A. The Person Of Ordinary Skill In The Art For the ’638 Patent.

400. As of the relevant time, a POSA for the ’638 Patent would have been a scientist with a Ph.D. in a field such as chemistry, medicinal chemistry, solid-state chemistry, pharmaceutics, pharmacology or the like, with one or two years of experience in the research, development, or characterization of pharmaceutical compounds, including chiral synthesis and resolution of stereomeric compounds or analytical methods (e.g., X-ray crystallography) for characterizing solid materials, or with an M.S. or similar degree and an additional three or more years of experience in the research, development, or characterization of pharmaceutical compounds. (Gribble Tr. 587:11-588:1; DDX2-21.)

401. Chiral synthesis and resolution are a normal part of one’s chemistry studies. When a POSA takes a course on organic chemistry, including during their sophomore year, they will be exposed to the principles of chiral synthesis, resolution, racemization. (Gribble Tr. 588:8-17; DDX2-21.)

402. Defendants' definition of a POSA is the correct definition of a POSA as it stays true to the subject matter of the '638 patent. (Gribble Tr. 587:13-588:1.)

403. Amgen proposed an alternative definition of a POSA that does not afford enough education or experience to a POSA. (Davies Tr. 1300:23-1301:11.)

B. The '638 Patent Priority Date Is March 20, 2002.

404. The earliest effective filing date for the '638 patent is March 20, 2002, the effective filing date of Provisional Application No. 60/366,515. (Gribble Tr. 616:22-617:7; DDX2-58; JTX-3.1)

405. There is no evidence that the inventors of the '638 patent conceived of a "pharmaceutical composition comprising stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione" that is "suitable for oral administration" in amounts of "10 mg to 200 mg," as required by the asserted claims, by October 21, 1999. (Gribble Tr. 616:22-617:3; Davies. Tr. 1302:17-18, 1475:15-22; DDX2-58.)

406. There is no evidence that the inventors understood how stereomerically pure apremilast would be formulated for oral administration, let alone whether the inventors understood what dose of stereomerically pure apremilast would be suitable for pharmaceutical use and treatment of inflammatory diseases. (Gribble Tr. 616:22-617:3; Davies. Tr. 1302:17-18, 1475:15-22; DDX2-58.)

407. Although the prior art as of October 1999 offered a wealth of information on formulating oral dosage forms, and it was known that stereomerically pure apremilast can be formulated into a tablet or capsule at a dose suitable for treating an inflammatory skin or arthritic condition, there is no evidence showing that the inventors of the '638 patent had the same understanding as of October 21, 1999. (Schafer Tr. 136:12-15.)

408. There is no evidence that the inventors were able to reduce to practice the full scope of the asserted claims of the '638 patent by October 21, 1999. (Gribble Tr. 616:22-617:3; DDX2-58.)

409. To the extent Amgen relies on *in vivo* data, such data does not demonstrate how the inventors were able to reduce to practice the asserted claims of the '638 patent, including pharmaceutical compositions comprising 10 to 200 mg (as recited in claim 6 of the '638 patent) of stereomerically pure apremilast. (Gribble Tr. 616:22-617:3; DDX2-58.)

410. As of 2002, there was also insufficient evidence that the (+)-enantiomer and the S-enantiomer are one and the same. The '638 patent only says that Compound A is "believed to be" the S-enantiomer. (JTX-3.7-8 (4:66-5:21).)

411. Dr. Man provided no testimony for the Court related to conception and reduction to practice of the asserted '638 patent claims. (Davies Tr. 1477:2-5.)

412. Dr. Schafer provided no testimony for the Court as to when he had a definite and permanent idea of the complete and operative invention. (Davies Tr. 1477:6-19.)

413. Dr. Schafer did not testify that the thousands of compounds synthesized in Celgene's drug discovery program were suitable for oral pharmaceutical compositions. (Davies Tr. 1477:25-1478:6); *see* Schafer Tr. 172:15-173:6 (testifying that his team at Celgene was testing "the hundreds, if not thousands, of compounds from the chemistry group" in order "to determine which compounds had the right pharmaceutical properties").)

414. Dr. Schafer did not testify that testing in a murine shock model assay was sufficient to show that apremilast would be useful for treating psoriasis. (Davies Tr. 1478:7-11; *see also see* Schafer Tr. 173:7-174:10 (testifying that "[t]he murine shock model was the very

first animal model that [they] would test the compounds in," and if a compound worked in this model, they would "go on to do further testing").))

C. The '638 Patent Claims Are Anticipated By The '358 Patent.

1. Each Element Of The Asserted Claims Is Disclosed In The '358 Patent.

415. The '358 patent discloses each element of claims 3 and 6 of the '638 patent: a pharmaceutical composition of stereomerically pure apremilast; with a pharmaceutically acceptable carrier, excipient, or diluent; suitable for oral administration; with dosages overlapping in the range from 10 to 200 mg. (Gribble Tr. 599:8-17; DDX2-35; DTX-174.)

a. Stereomerically Pure Apremilast

416. The '358 patent discloses "2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione" as the title compound in Example 12. (Gribble Tr. 591:18-23; DTX-174.9 (14:34-55).)

417. The '358 patent also discloses 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione as a compound of Formula I by disclosing that in Formula I, Y can be C=O; R^1, R^2, and R^3 can each be a hydrogen; R^4 can be NR^8R^9 where each of R^8 and R^9, taken independently of the other, can be a hydrogen and the other is $–COR^{10}$ where R^{10} is an alkyl of 1 to 8 carbons; R^5 and R^6, independently of the other, can be an alkoxy of 1 to 4 carbon atoms; and R^7 can be an alkyl of 1 to 8 carbons. (DTX-174.12 at claim 1, *see also id.* at 4:66–6:67.)

418. Example 12 is a compound of Formula I of the '358 patent. (Gribble Tr. 594:23-24; Davies Tr. 1398:16-20.)

419. Example 12 describes the synthesis of the racemic mixture that contains both the R and S enantiomers. (Davies Tr. 1478:20-1479:7.)

420. Example 12 of the ’358 patent is a racemic mixture that is 50% of the (+) isomer, which is apremilast, and 50% the (-) isomer. (Gribble Tr. 591:18-23; DDX2-29.)

421. When a POSA reads Example 12 of the ’358 patent, they immediately know that the compound is a racemate. (Gribble Tr. 591:22-592:9; DDX2-28; DDX2-29.)

422. Based on the chemical name of Example 12, a POSA would know that Example 12 is a racemate. (Davies Tr. 1398:2-10.)

423. A POSA would know that the racemate of Example 12, and the two enantiomers of the racemate, have the same atom-to-atom connection. (Davies Tr. 1400:25-1401:4.)

424. Based on the chemical name of Example 12, a POSA would know the chemical formula of the two enantiomers. (Davies 1401:5-16.)

425. A POSA would understand the synthetic method described in Example 12 to necessarily result in a racemic mixture that is 50% apremilast. (Gribble Tr. 591:22-593:16; DDX2-28; DDX2-29.)

426. The ’358 patent discloses both enantiomers of Example 12, both the (+) and (-) isomers of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. (Gribble Tr. 591:22-593:16; DDX2-28; DDX2-29.)

427. The ’358 patent discloses that in compounds of Formula I, “the carbon atom designated * constitutes a center of chirality.” (DTX-174.5 (5:1-16).)

428. The ’358 patent claims compounds of Formula I in claim 1. (DTX-174.12 (20:60-61).)

429. Claim 1 of the ’358 patent indicates that the compounds of Formula I have a single, chiral carbon and identify that chiral carbon in the chemical structure of Formula I compounds. (DTX-174.12 (20:60-61).)

430. Claim 1 of the '358 patent covers apremilast. (Gribble Tr. 598:23-599:5; Davies Tr. 1492:12-25; Vellturo Tr. 388:16-389:2; DDX2-24; DTX-174.12 (20:15-29).)

431. Claim 18 of the '358 patent claims "[a] method of inhibiting PDE IV in a mammal which comprises administering thereto an effective amount of a compound according to claim 1." (Gribble Tr. 598:23-599:4; DDX2-34; DTX-174.12-13 (20:15-65, 22:33-35).)

432. The '358 patent explicitly discloses that "[t]he compounds of Formula I possess a center of chirality and can exist as optical isomers. Both the racemates of these isomers and the individual isomers themselves, as well as diastereomers when there are two chiral centers, are within the scope of the present invention." (Gribble Tr. 594:6-22; Davies Tr. 1406:23-1408:7; DDX2-29; DDX2-30; DTX-174.6 (8:63-67).)

433. The '358 patent explicitly discloses separation and purification of isomers of Formula I compounds, including apremilast:

> The racemates can be used as such or can be separated into their individual isomers mechanically as by chromatography using a chiral absorbant. Alternatively, the individual isomers can be prepared in chiral form or separated chemically from a mixture by forming salts with a chiral acid, such as the individual enantiomers of 10-camphorsulfonic acid, camphoric acid, α-bromocamphoric acid, methoxyacetic acid, tartaric acid, diacetyltartaric acid, malic acid, pyrrolidone-5 carboxylic acid, and the like, and then freeing one or both of the resolved bases, optionally repeating the process, so as to obtain either or both substantially free of the other, i.e., in a form having optical purity of >95%.

(Gribble Tr. 594:6-22; DDX2-29; DDX2-30; DTX-174.6-7, 9 (8:67-9:12, 14:34-55).)

434. A POSA would have understood the disclosure in the '358 patent concerning the separation and purification of isomers of Formula I to apply to Example 12 and the purification of stereomerically pure apremilast. (Gribble Tr. 595:10-25; DDX2-31; DTX-174.6-7, 9 (8:63-9:12, 14:35-55).)

435. Separation of individual isomers mechanically by chromatography using a chiral absorbant is a common technique. (Gribble Tr. 595:10-596:11.)

436. Of the possible methods available for separating the isomers of Example 12, chiral chromatography was the simplest and most widely used as of the effective filing date of the '638 patent. (Gribble Tr. 595:10-596:11.)

437. Chiral chromatography would have been a POSA's first choice as a separation technique for the individual isomers of Example 12. (Gribble Tr. 595:10-596:11.)

438. The result of separating individual isomers of Example 12 mechanically by chromatography using a chiral absorbant would be apremilast, substantially free of the other isomer and in form having an optical purity greater than 95%. (Gribble Tr. 595:10-596:11; DDX2-31.)

439. A POSA following Example 12 and the instructions shown in columns 8 and 9 of the '358 patent regarding separation and purification of isomers using chiral chromatography would have necessarily obtained stereomerically pure apremilast having greater than 98% by weight of apremilast. A POSA may have performed a second run through the column to enhance the purity, which is a standard and routine part of the art. (Gribble Tr. 596:12-20.)

440. A second run of the column to further purify the isomers of Example 12 would be performed by taking additional fractions or elutions that contain the apremilast enantiomer and re-chromatograph those on the column in order to obtain additional separation of the enantiomers. (Gribble Tr. 596:21-597:4.)

441. Obtaining an optical purity of greater than 98% of an isomer, such as apremilast, is not a difficult task for a person of skill in the art. (Gribble Tr. 597:5-8.)

442. Obtaining an optical purity of greater than 98% of an isomer, such as apremilast, would be a routine experiment for a person of skill in the art. (Gribble Tr. 597:9-12.)

443. There is no considerable difference between the optical purity disclosed in the '358 patent, greater than 95%, and that claimed in the asserted patents, which is greater than 98%. A purity of greater than 95% includes greater than 98%. (Gribble Tr. 597:13-18.)

444. A person of skill in the art would have had the knowledge and experience to separate the enantiomers of Example 12. (Gribble Tr. 597:19-598:3.)

445. Chromatography is a general separation technique taught at a very early stage of a POSA's education. (Gribble Tr. 597:19-598:3.)

446. Chiral chromatography employs the same techniques as chromatography where the only difference is the adsorbent is chiral as opposed to achiral. (Gribble Tr. 597:19-598:3.)

447. The '358 patent's recitation of the compounds of Formula I having an "optical purity >95%" is a recitation of stereomerically pure apremilast substantially free of the (-) enantiomer. (Gribble Tr. 589:7-590:9; DDX2-23; DDX2-24; ECF No. 187 (Agreed-to Claim Constructions).)

448. Under the '638 and '536 patent's definition of "stereomerically pure," stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione substantially free of its (-) isomer, has "most preferably greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound." (JTX-3.8 (6:29-32); JTX-7.8 (6-9).)

449. The '358 patent's recitation of the compounds of Formula I having an "optical purity >95%" is a recitation of stereomerically pure apremilast substantially free of the (-) enantiomer, including greater than about 97% by weight of the (+) enantiomer and less than

about 3% by weight of the (-) enantiomer. (Gribble Tr. 589:5-590:5; DDX2-23; DDX2-24; ECF No. 187 (Agreed-to Claim Constructions); JTX-3.8 (6:29-32); JTX-7.8 (6-9).)

450. The '358 patent discloses the racemate, 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, as a compound of Formula I, and that compounds of Formula I "exist as optical isomers" and "can be separated into their individual isomers mechanically as by chromatography using a chiral absorbant" or "the individual isomers can be prepared in chiral form or separated chemically from a mixture" in order to obtain a composition that comprises one stereoisomer of a compound substantially free of other stereoisomers of that compound, "i.e., in a form having optical purity of >95%." (JTX-174.6-7, 9 (8:67–9:12, 14:34-55).)

451. The '358 patent discloses both enantiomers of Example 12, both the (+) and (-) isomers of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, that the enantiomers can be separated to substantially purity, and methods to achieve such. (JTX-174.6-7, 9 (8:67–9:12, 14:34-55).)

452. A POSA reading the '358 patent would have been familiar with racemic pharmaceutical compounds. (Gribble Tr. 579:5-13, 580:1-6, 581:5-19; DDX2-14; DDX2-15; JTX-133.20; JTX-134.1.)

453. A POSA reading the '358 patent would have understood that both the (+) and (-) isomers of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione are explicitly disclosed in the '358 patent due to all compounds of Formula I in the '358 patent existing as optical isomers and having an identified chiral carbon. (Gribble Tr. 591:24-592:9; DDX2-29.)

454. A POSA reading the '358 patent would have understood the disclosure of "2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione" in Example 12 as a disclosure of a racemic mixture containing a 50:50 molar ratio of "(+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione" and "(-)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione." (Gribble Tr. 591:24-593:16; DDX2-29.)

455. A POSA reading the '358 patent would have understood the '358 patent as disclosing methods to obtain stereomerically pure compounds of Formula I, including the (+) and (-) isomers of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, with an optical purity of >95%. (Gribble Tr. 591:24-598:3; DDX2-28-31.)

456. A POSA reading the '358 patent would have known various methods to obtain a single stereoisomer substantially free of the other isomer, including various separation techniques. (Gribble Tr. 582:17-584:16; DDX2-17; JTX-133.20-22; JTX-185.5-12; JTX-183.12-19.)

457. A POSA would have understood the '358 patent as disclosing the use of chiral column chromatography as a method to obtain stereomerically pure isomers of compounds of Formula I, including stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione substantially free of (-)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. (Gribble Tr. 596:1-11; DDX2-17-18.)

458. A POSA would have been familiar and experienced with chiral column chromatography as a method to separate chiral compounds in a racemate in order to obtain one

stereoisomer substantially free of the other stereoisomer. By 2002, chiral chromatography was known to result in optical purities of greater than 99%, and that higher levels of purity could be obtained by re-running an elution through the column. (Gribble Tr. 596:1-597:12 .)

459. A POSA would have understood the '358 patent as disclosing separation of the (+) and (-) isomers of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or preparation of one isomer with subsequent purification, until one isomer can no longer be detected. (Gribble Tr. 594:8-595:25; Davies Tr. 1459:1-5; DDX2-30; DTX-174.7 (9:10-12).)

460. The '358 patent instructs a POSA to repeat the separation techniques, "so as to obtain either or both substantially free of the other, i.e., in a form having optical purity >95%." (Gribble Tr. 596:12-20; DTX-174.7 (9:10-12).)

461. Therefore, the '358 patent explicitly discloses stereomerically pure apremilast. The compound (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione having optical purity of >95% would be stereomerically pure and would be substantially free of the (-) isomer. (Gribble Tr. 594:8-596:20.)

462. Stereomerically pure apremilast is inherently disclosed by the '358 patent. A POSA reading the '358 patent would immediately envisage stereomerically pure apremilast in the '358 patent. (Gribble Tr. 594:8-596:20; Davies Tr. 95:14-25, 1315:18-25, 1396:23-1397:9, 1400:25-1401:4, 1401:13-16, 1403:25-1404:3.)

463. The chemical structure of apremilast is inherently disclosed by Example 12 in the '358 patent. (Gribble Tr. 624:22-25.)

464. A POSA would understand Example 12 of the '358 patent to be one-half apremilast without the need for the '358 patent to name apremilast in particular. (Gribble Tr.

630:11-17.) Dr. Davies testified that the '358 patent fails to identify apremilast because the '358 patent does not state the optical rotation of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, namely, (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. (Davies Tr. 1396:14-1397:1.)

465. Claims 3 and 6 of the '638 patent, and claim 6 of the '536 patent, do not use the name "apremilast," and instead use the chemical name of the compound, 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, with the indication that this is the (+) isomer. (Davies Tr. 1395:17-19.)

466. The (+) before 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione indicates that the compound is an enantiomer. (Davies Tr. 1396:16-18.)

467. The name 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione was in the prior art before the filing of the '638 and '536 patent applications. (Davies Tr. 1396:14-1397:9.)

468. The name 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione was publicly disclosed in Example 12 of the '358 patent before the filing of the '638 and '536 patent applications. (Davies Tr. 1396:14-1397:9, 1397:24-1398:1.)

469. The disclosure of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione in the '358 patent is the same as a disclosure of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione and (-)2-

[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. (Gribble Tr. 591:18-598:3; DDX2-28-30.)

470. A POSA reading the '358 patent would have known that 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione is a 50:50 mixture of the (+)- and (-) isomers, and a POSA seeing a recitation of preparing 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione in Example 12 would have immediately envisaged (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. (Gribble Tr. 591:18-598:3; DDX2-28-30; Davies Tr. 95:14-25, 1315:18-25, 1396:23-1397:9, 1400:25-1401:4, 1401:13-16, 1403:25-1404:3.)

471. A POSA also would have immediately envisaged stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione based on the disclosure in the '358 patent that individual isomers are within the scope of the '358 patent, and can be prepared or separated to a form having an optical purity >95%. (Gribble Tr. 591:18-598:3; DDX2-28-30; DTX-174.6-7 (8:63-9:12; 14:34-55).)

472. The '358 patent also explicitly discloses pharmaceutically acceptable salts of compounds of Formula I. (DTX-174.7 (9:13-21).)

473. The '358 patent expressly discloses "a pharmaceutically acceptable salt, solvate, or hydrate" and "a pharmaceutically acceptable metabolite, salt, solvate, or hydrate" of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, as recited in the asserted claims of the '638 patent. (DTX-174.7 (9:13-21).)

474. The physical and biological properties of apremilast, including solubility and TNF-alpha PDE IV inhibition potency, are inherently disclosed in the '358 patent. (Gribble Tr. 625:13-628:1.)

b. Pharmaceutical Compositions

475. The '358 patent discloses pharmaceutical compositions comprising compounds of the Formula I associated with at least one pharmaceutically acceptable carrier, diluent or excipient. (Gribble Tr. 598:4-14; DDX2-32; DTX-174.7 (9:31-34).)

476. The '358 patent instructs that to prepare oral pharmaceutical compositions of compounds of Formula I:

> the active ingredients are usually mixed with or diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule or sachet. When the excipient serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, carrier, or medium for the active ingredient. Thus the compositions can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

(DTX-174 (9:34-43).)

477. The '358 patent instructs what would be "suitable excipients" for compounds of Formula I:

> lactose, dextrose, sucrose, sorbitol, mannitol, starch, gum acacia, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidinone, cellulose, water, syrup, and methyl cellulose, the formulations can additionally include lubricating agents such as talc, magnesium stearate and mineral oil, wetting agents, emulsifying and suspending agents, preserving agents such as methyl- and propylhydroxybenzoates, sweetening agents or flavoring agents.

(DTX-174 (9:43-52).)

478. The '358 patent discloses that compositions comprising compounds of Formula I can be formulated "with a suitable pharmaceutical excipient" in dosage forms "containing a

predetermined quantity of active material calculated to produce the desired therapeutic effect." (DTX-174.7 (9:53–60).)

479. The '358 patent discloses oral dosage forms comprising compounds of Formula I, including tablets and capsules, containing from 1 to 100 mg of drug per unit of dosage form. (DDX2-30; DTX-174.7 (9:22–24).)

480. The '358 patent contains Examples formulating compounds of Formula I into tablets containing 50 mg (Example 21), 100 mg (Example 22), 75 mg (Example 23), and 10 mg (Example 24), and a capsule containing 100 mg (Example 25). (DTX-174.11-12 (17:44 – 19:56).)

481. A POSA would have understood the '358 patent to disclose oral pharmaceutical compositions of stereomerically apremilast. There is nothing novel about the pharmaceutical composition recited in the claims of the '638 patent, and Dr. Davies was not asked to provide an opinion on the pharmaceutical composition. (Gribble Tr. 598:4-14; Davies Tr. 1393:24-1395:13.)

482. There is no considerable difference between the claimed ranges of dose amounts of apremilast in the '638 patent and the dose amounts disclosed in the '358 patent, and a POSA reading the '358 patent would immediately envisage 10 to 200 mg of a Formula I compound, including stereomerically pure apremilast. (Gribble Tr. 599:10-17; JTX-3.21 (32:9-12); DTX-174.7 (9:22-24).)

2. The '358 Patent Enabled Separation Of The Enantiomers.

483. A POSA would have been able to separate the (+) and (-) isomers of Example 12 of the '358 patent with routine experimentation. (Gribble Tr. 593:4-594:5, 596:12-20, 597:5-12, 603:19-604:11; DDX2-18; DDX2-29; JTX-133.20-22; JTX-181.5-12; JTX-183.12-19.)

484. Separation of enantiomers using chiral chromatography is routine, standard experimentation taught in sophomore organic chemistry, and was initially discovered in 1906. (Gribble Tr. 582:18-584:12; 593:4-594:5.)

485. Simply looking at Example 12 in the '358 patent, a POSA would know how to separate the enantiomers, one of which is apremilast. (Gribble. Tr. 640:20-641:1.)

486. Dr. Davies testified that it would be undue experimentation for a POSA to make stereomerically pure apremilast because a POSA may "never be able to make" stereomerically pure apremilast. (Davies Tr. 1385:23-1386:6.) Dr. Davies cites no articles, publications, or authorities to support his opinion that separation of enantiomer is a long, huge effort with no expectation of success. (Davies Tr. 1431:21-1432:15.)

487. Dr. Davies's own publication states that it is a good idea to separate enantiomers. (Davies Tr. 1432:22-1433:4; DTX-485.6.) Dr. Davies's own publication states that "the differing pharmacological effects of the two enantiomers of chiral molecules are now well documented." (Davies Tr. 1434:3-12; DTX-485.6.)

488. Dr. Davies testified that his opinion that it would be undue experimentation for a POSA to make stereomerically pure apremilast was based on the *Wands* factors. (Davies Tr. 1386:9-24.)

489. Dr. Davies testified that in his personal, business experience, they never "promised to produce a single enantiomer" but "still [] did extremely well." (Davies Tr. 1490:2-23.)

490. By 2002, "the number of chiral stationary phases available for the separation of enantiomers [had] grown rapidly." (Davies Tr. 1436:5-1437:2; JTX-182.2.)

491. By 2002, "the most efficient and flexible approach for generation of pure enantiomers [was] still batch chromatography … This technique allows one to easily scale up to the amounts needed in the different phases of drug discovery." (Davies Tr. 1437:13-1438:7; JTX-182.3-4.)

492. Chromatography can be scaled up to obtain adequate amounts of compound by increasing the size of the column combined with throughput improving techniques. (Davies Tr. 1438:8-18; JTX-182.3-4.)

D. The '638 Patent Claims Are Obvious.

493. A POSA would have looked to and found the '358 patent when interested in finding new PDE IV inhibitors. (Gribble Tr. 601:22-602:3, 603:3-10; DDX2-41.)

494. A POSA looking for a PDE4 inhibitor would have started with the '358 patent and looked to the 17 examples of the '358 patent, made those compounds, separated the enantiomers, and tested those. A POSA would have arrived at apremilast because it is one of the enantiomers of those examples. (Gribble Tr. 654:7-15; DDX2-41.)

495. A POSA would have considered the Example compounds of the '358 patent to be the important compounds of Formula I to consider as PDE IV inhibitors. (Gribble Tr. 655:7-19; DDX2-41.)

496. Based on the statement in the '358 patent that inhibition of PDE IV is particularly effective for the disclosed compounds, a POSA would focus on inhibition of PDE IV and not PDE III. Dr. Davies testified that the '358 patent also discusses decreasing TNF-alpha levels and Celgene's internal testing showed that Example 12 is the most active compound to inhibit TNF-alpha. (Gribble Tr. 656:13-21; Davies Tr. 1414:23-1416:23; PTX11-15.)

497. The compounds of Formula I are thalidomide analogs only to the extent that the compounds contain a phthalimide ring as thalidomide does. (Gribble Tr. 657:24-658:4.)

498. A POSA would have been interested in Example 12 of the '358 patent because it is one of only 17 examples of Formula I compounds in the '358 patent. Rather than go to the billions of compounds encompassed by Formula I, a POSA would go to the 17 examples, look at those and synthesize those, separate the enantiomers, and test for inhibition of PDE IV. (Gribble Tr. 603:21-604.11; DDX2-41.)

499. A POSA would have considered all 17 Example Formula I compounds in the '358 patent. (Davies Tr. 1419:9-15.)

500. Separating the (+) and (-) isomers of Example 12 requires no chemical modification of Example 12. (Gribble Tr. 592:21-594:5.)

501. An example of a chemical modification of Example 12 is separation of the enantiomers using chiral acid salt separation where the acetyl group on the phthalimide group of Example 12 is changed to an amine by hydrolysis before starting the chiral acid-base reaction (Gribble Tr. 644:15-646:3; DTX-174.9 (14:34-55).)

502. Separating the (+) and (-) isomers of Example 12 is a physical or mechanical separation. (Gribble Tr. 592:21-594:5.)

503. Drug discovery using a lead compound includes identifying a lead compound, testing it, making a change to one part of the molecule, retesting it, making another change to part of the molecule, and retesting it again. (Gribble Tr. 651:15-19.)

504. The '358 patent discloses a limited and finite number of compounds that a POSA would understand are useful as lead compounds that could be tested in a routine manner to identify the most promising PDE4 and TNF-α inhibitors. (Gribble Tr. 603:21-604:11.)

505. WO 01/34606 ("WO '606"), "Pharmaceutically Active Isoindoline Derivatives," published on May 17, 2001. (DTX-159.1.)

506. WO ’606 discloses isoindoline derivatives that decrease the levels of TNFα and inhibit phosphodiesterases, particularly PDE4. (DTX-159.2 (1:6–9).)

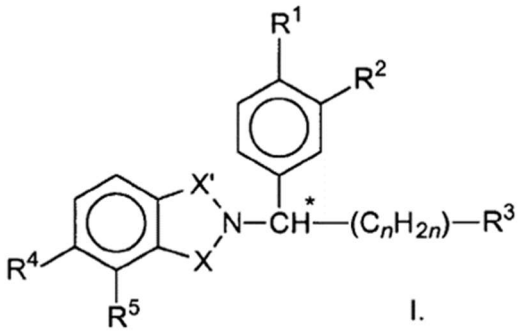
507. WO ’606 reinforces the teachings of the ’358 patent, teaches compounds of a Formula I that are useful for inhibiting PDE IV, and teaches to separate these compounds into the individual enantiomers such that each are substantially free of the other enantiomer. (Gribble Tr. 605:23-606:10; DDX2-42; DTX-159.11-12 (10:2-11:23), DTX-159.20-21 (19:21-20:9), and DTX-159.25 (24:1-8).)

508. WO ’606 teaches that the compounds of Formula I can be assayed conveniently using methods known in the art. (Gribble Tr. 605:23-606:10; DDX2-42; DTX-159.21-22 (20:6-21:29).)

509. WO ’606 teaches that the disclosed isoindoline derivatives are useful for treating diseases mediated by PDE4 inhibition, including inflammation and autoimmune diseases, as well as psoriasis and rheumatoid arthritis, “with a minimum of unwanted side effects.” (Gribble Tr. 605:23-606:10; DDX2-42; DTX-159.2 (1:11–15), DTX-159.10 (9:10–28), DTX-159.23 (22:27-29), and DTX-159.24 (23:8-24).)

510. WO ’606 discloses that the invention relates to pharmaceutical compositions and discloses oral dosage forms, including tablets and capsules containing from 1 to 100 mg of Formula I compounds per unit dosage. (Gribble Tr. 605:23-606:10; DDX2-42; DTX-159.25 (24:1-3).)

511. WO ’606 discloses compounds of Formula I, where the carbon atom designated with a * constitutes a center of chirality:



I.

(Gribble Tr. 605:23-606:10; DDX2-42; DTX-159.11 (10:1–4).)

512. WO '606 discloses that in Formula I, R^1 and R^2 can each be alkoxy groups having 1 to 4 carbon atoms, X and X' can be C=O groups, n can have a value of 1, R^3 can be $–SO_2$-Y where Y is an alkyl of 1 to 6 carbon atoms, R^4 can be a hydrogen, R^5 can be $NR^6R^7C_zH_{2z}$ where z can be zero, R^6 can be an alkanoyl of 2 to 5 carbons, and R^7 can be a hydrogen. (*Id*. at 10:5–12:12.) WO '606 also discloses that the invention pertains to acid addition salts of these isoindoline derivatives. (DTX-159.13 (12:13-19).)

513. WO '606 states that the compounds of Formula I "preferably are administered as a substantially chirally pure isomer, (S)- or (R)-, but can also be [a]dministered as a mixture of the (S)-isomer and the (R)-isomer." (Gribble Tr. 606:13-20, 607:1-9; DTX-159.13 (12:20–22).)

514. WO '606 states that the "compounds possess a center of chirality and thus can exist as optical isomers. Both the chirally pure (R)- and (S)-isomers as well as mixtures (including but not limited to racemic mixtures) of these isomers, as well as diastereomers when there are two chiral centers, are within the scope of the invention." (Gribble Tr. 605:23-606:10; DDX2-42; DTX-159.20 (19:21-25).)

515. WO '606 states that the mixture of optical isomers of the compounds of Formula I "can be separated into their individual isomers mechanically as by chromatography using a chiral absorbent. Alternatively, the individual isomers can be prepared in chiral form or separated

chemically from a mixture by forming salts with a chiral acid" and then "freeing one or both of the resolved bases." (Gribble Tr. 605:23-606:10; DDX2-42; DTX-159.20 (19:25-29), DTX-159.21 (20:3-4).)

516. WO '606 states that the separation process can be repeated "so as to obtain [one isomer] substantially free of the other, i.e., in a form having an optical purity of >95%." (Gribble Tr. 605:23-606:10; DDX2-42; DTX-159.21 (20:4-5).)

517. WO '606 states that inhibition of PDE4 by the compounds of Formula I "can be conveniently assayed using methods known in the art, e.g., enzyme immunoassay, radioimmunoassay, immunoelectrophoresis, affinity labeling, etc., of which the following are typical." (DTX-159.21 (20:6-9).) WO '606 discloses assays including LPS stimulated PBMC and PDE4 (U937 cell-derived) enzyme assay. (DTX-159.21-22 (20:10-21:29).)

518. WO '606 discloses "pharmaceutical compositions in which (i) a quantity of a substantially chirally pure (R)- or (S)-isomer of a compound of Formula I or a mixture of those isomers, that upon administration in a single or multiple dose regimen is pharmaceutically effective is combined with a pharmaceutically acceptable carrier." (DTX-159.24 (23:25–29).)

519. WO '606 discloses oral dosage forms, including capsules and tablets, containing from 1 to 100 mg of drug per unit dosage. (DTX-159.25 (24:1–3).) WO '606 discloses examples of suitable excipients for tablets and pills. (DTX-159.25 (24:9-26).)

520. WO '606 also discloses that the compounds of Formula I are preferably formulated in unit dosage form, "meaning physically discrete units suitable as a unitary dosage, or a predetermined fraction of a unitary dose to be administered in a single or multiple dosage regimen to human subjects and other mammals, each unit containing a predetermined quantity of

active material calculated to produce the desired therapeutic effect in association with a suitable pharmaceutical excipient." (DTX-159.25-26 (24:27–25:4).)

521. In Examples 39-42, WO '606 discloses preparation of tablets containing 50 mg, 100 mg, 75 mg, or 10 mg of compounds of Formula I. (DTX-159.52-54 (51:11-53:23).) In Example 43, WO '606 discloses preparation of a gelatin dry-filled capsule containing 100 mg of a compound of Formula I. (DTX-159.55-56 (54:21-55:17).)

522. Claim 1 of WO '606 recites a compound of Formula 1, and claim 31 recites "[t]he method of inhibiting PDE IV in a mammal which comprises administering thereto an effective amount of a substantially chirally pure (R)- or (S)-isomer of a compound according to Claim 1 or a mixture of said isomers." (DTX-159.86-88, 93 (85:1-87:7, 92:1-3).)

523. Claim 34 of WO '606 recites "[a] method of treating in a mammal a disease selected from the group consisting of inflammatory disease, autoimmune disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, … asthma …, which comprises administering thereto an effective amount of a substantially chirally pure (R)- or (S)-isomer of a compound according to Claim 1 or a mixture of said isomers." (DTX-159.93 (92:12-18).)

524. Claim 37 of WO '606 recites "[a] pharmaceutical composition comprising (i) a quantity of a substantially chirally pure (R)- or (S)-isomer of a compound according to Claim 1 or a mixture of said isomers, that upon administration in a single or multiple dose regimen is pharmaceutically effective and (ii) a pharmaceutically acceptable carrier therefor." (DTX-159.93 (92:25-28).)

525. Dr. Gribble is not convinced that Example 12 is excluded from Formula I of WO '606. (Gribble Tr. 677:24-678:9.)

526. A POSA reading the '358 patent would have looked to WO '606 because WO '606 reinforces the teachings of the '358 patent by teaching oral pharmaceutical compositions containing Formula I compounds, and that preferably the compounds are administered as a substantially chirally pure isomer, and also teaches biological assays and protocols to test the isomers for inhibition of PDE IV. (Gribble Tr. 606:11-20; DDX2-43.)

527. The combined disclosures of the '358 patent and WO '606 teach all elements of claims 3 and 6 of the '638 patent. (Gribble Tr. 608:15-23; DDX2-45.)

528. Takeuchi, *et al*., "(R)- and (S)-3-Fluorothalidomides: Isosteric Analogues of Thalidomide," *Organic Letters*, 1(10), 1571–1573, published in 1999. (DTX-168.1.)

529. Takeuchi discloses preparation of 3-fluorothalidomide, "a nonracemizable analogue of thalidomide." (DTX-168.1 at Abstract.) Takeuchi discloses that "[i]n strategies designed to develop drugs that might have *the* beneficial effects of thalidomide without the teratogenic side effects, synthesis of nonracemizable analogues of thalidomide has attracted much attention." (DTX-168.1 (emphasis added).)

530. Takeuchi discloses optical resolution of racemic compound 3 by HPLC using a chiral column, Diacel Chiralcel AD, eluting with ethanol. "Each enantiomer was obtained with an optical purity of more than 99% ee." (DTX-168.2.)

531. Takeuchi teaches preparation of 3-fluorothalidomide where the fluorine replaces the unstable hydrogen molecule in thalidomide, and teaches that this compound does not racemize. (Gribble Tr. 609:10-23; DDX2-47.)

532. Takeuchi teaches separation of the R- and S- enantiomers of 3-fluorothalidomide using a commercial chiral column and eluting with ethanol as the solvent, and that each

enantiomer was obtained with an optical purity of more than 99% ee. (Gribble Tr. Tr. 609:12-610:4; DDX2-47.)

533. A POSA reading the '358 patent would have looked to Takeuchi because it teaches separation of enantiomers of a compound that has a phthalimide ring, just as disclosed in the '358 patent, and because Takeuchi teaches separation of the enantiomers to greater than 99% purity and subsequent biological testing of each enantiomer. The combined disclosures of the '358 patent and Takeuchi teach all elements of claims 3 and 6 of the '638 patent. (Gribble Tr. 610:6-15, 612:4-11; DDX2-47, 50.)

1. Motivation

534. One reason people of skill were interested in obtaining individual enantiomers as pharmaceutical compounds was because one enantiomer of a racemate may be useful in treating a disease while the other enantiomer can be harmful to humans. (Davies Tr. 1434:15-23.)

535. "Thalidomide has frequently been used as an example to highlight the dangers of racemates and to promote the case for pure enantiomer development." (JTX-134.1.)

536. "There is no doubt that there are strong compelling reasons to develop single enantiomers," including the reasons of: "1. Therapeutic activity resides principally in one enantiomer, 2. Low therapeutic index, 3. Toxicity associated with distomer, 4. No chiral inversion, 5. Economic feasibility." (Davies Tr. 1440:20-1442:7; JTX-180.130-31.)

537. "The enantiomer vs. racemate issue is still being termed a 'debate.' It is the author's view that a debate no longer exists. The science is well recognized. The chemical and analytical technology has seen dramatic advances in the past decade. Basic scientists, pharmaceutical developers, and regulatory authorities are well aware of the issues. Development of a single enantiomer is wise and prudent. Patients would not be exposed to a drug mixture." (Davies Tr. 1442:8-1443:24; JTX-180.134.)

538. "[T]ype I CSPs [chiral stationary phases] have been used to stereochemically resolve a vast number of compounds." (Davies Tr. 1444:5-1445:13; JTX-180.25-26.)

539. The prior art taught to separate the enantiomers of thalidomide and thalidomide analogs. (Davies Tr. 1450:20-1459:5; DDX2-53; JTX-239.1; JTX-68.1, 4; DTX-168.1.)

540. Example 12 is a racemic mixture and thalidomide analog. (Davies Tr. 1450:20-23, 1459:21-1460:3.)

541. If a POSA separated the enantiomers of Example 12, the S-enantiomer would be apremilast. (Davies Tr. 1459:21-1460:7.)

542. A POSA would have been motivated with a reasonable expectation of success to separate the enantiomers of Example 12. Any time a POSA has a racemic mixture, the POSA is motivated to separate the isomers so that there is no longer a mixture of two things. (Gribble Tr. 604:18-605:3.)

543. A POSA would have been motivated with a reasonable expectation of success to test each enantiomer of Example 12, and any racemic mixture in any situation, in order to determine the relative biological activity of each. There is never not a motivation to separate racemic mixtures. A POSA would have understood that one isomer can be pharmaceutically or biologically active, and the other isomer can result in adverse effects or toxicity (or have no activity), and a POSA would have preferred a stereomerically pure compound over the racemate as a pharmaceutical agent. (Gribble Tr. 604:18-605:3; DTX-118; DTX-119.)

544. A POSA would have been motivated to separate the enantiomers of Example 12 because the POSA would not know which enantiomer is more potent, and therefore would be motivated to first separate the enantiomers and then test each for inhibition of PDE IV. (Gribble Tr. 605:2-9.)

545. If a POSA first tests the racemate and finds the activity to be sufficiently poor, the POSA would be motivated to separate the enantiomers and test each for biological activity. (Gribble Tr. 605:10-14.)

546. WO '606 adds to a POSA's motivation to separate the enantiomers of Example 12 of the '358 patent because WO '606 teaches that compounds of Formula I preferably are administered as substantially chirally pure isomers. (Gribble Tr. 607:1-9; DDX2-43.)

547. Takeuchi adds to a POSA's motivation to separate the enantiomers of Example 12 because Takeuchi was able to separate the enantiomers of 3-fluorothalidomide to 99% optical purity, and these compounds are related to apremilast via the phthalimid ring structure, and Takeuchi teaches to test each enantiomer for biological activity and finds that one enantiomer is more active than the other. (Gribble Tr. 610:22-611:4; DDX2-47.)

2. Reasonable Expectation Of Success.

548. A POSA would have reasonably expected apremilast to be one of the enantiomers of Example 12. A POSA would know that Example 12 could be separated into individual isomers, and POSA would test each isomer individually and would then discover apremilast had greater activity than the other enantiomer. (Gribble Tr. 604:12-17; DDX2-41.)

549. The '358 patent and WO '606 discuss the same art (PDE4 inhibitors), useful for the same diseases and conditions (including psoriasis), disclose a Formula I with isomers that include apremilast, teach how to make oral pharmaceutical compositions out of these compounds with pharmaceutically acceptable carriers or excipients, and have, on their faces, the same assignee (Celgene). (DTX-174.1, 4-5, 7; DTX-159.1-3, 9-12, 25 ; DDX2-44.)

550. A POSA would have been motivated by the combined teachings of the '358 patent and WO '606 to separate the enantiomers of Example 12 and would have reasonably expected to obtain optical purity greater than 98%. Possessing the pure enantiomers, the POSA

would have been motivated by the combined teachings of the '358 patent and WO '606 to test both enantiomers for PDE4 inhibition and then reasonably would have expected that one or both of these enantiomers would inhibit PDE4. (Gribble Tr. 607:10-23; DDX2-44.)

551. Dr. Gribble also noted that a POSA would have been motivated with a reasonable expectation of success to isolate the individual isomers of the racemate disclosed in Example 12 of the '358 patent based on its teachings combined with that of WO '606, and then study the pharmacological activity of each isomer compared to each other and to the racemate. (Gribble Tr. 604:12-17.)

552. A POSA with the optically pure enantiomers of Example 12 would have been motivated by the combined teachings of the '358 patent and WO '606 to formulate apremilast into an oral pharmaceutical composition containing anywhere from 10 to 200 mg of the stereomerically pure enantiomers with a reasonable expectation of success. The combination of the '358 patent and WO '606 was not considered by the Patent Office during prosecution of the '638 patent. (Gribble Tr. 607:10-608:12; DDX2-44; JTX-16.)

553. A POSA would have been motivated with a reasonable expectation of success to arrive at the subject matter of claims 3 and 6 of the '638 patent based on the combined teachings of the '358 patent and Takeuchi, which teach to separate enantiomers to 99% stereomeric purity and test and formulate the enantiomers into oral dosage forms in the range of 10 to 200 mg. The combination of the '358 patent and Takeuchi was not considered by the Patent Office during prosecution of the '638 patent. (Gribble Tr. 611:7-19; DDX2-48; JTX-16.)

554. The '638 patent states that the enantiomers of Example 12 can be separated using known techniques. (Davies Tr. 1460:9-1464:21, 1465:18-1467:23, 1468:8-25, 1469:16-1471:12; JTX-3.10 (9:8-24).) Statements to a patent office made during prosecution of a patent

application and concerning the scope of prior art are binding admissions in subsequent litigation. *See Procter & Gamble Co. v. Nabisco Brands, Inc.*, 711 F. Supp. 759, 770 (D. Del. 1989) ("a patentee's representations to the [Patent Office] during the prosecution of its patent application about the scope of the prior art is a binding admission and should 'be accepted at face value' during subsequent litigation over the patent.").

555. The '638 patent states that the racemate "is readily prepared using the methods in U.S. Pat[ent] No. 6,020,358, which is incorporated herein by reference. Compound A [apremilast] can be isolated from the racemic compound by techniques known in the art. Examples include, but are not limited to, the formation of chiral salts and the use of chiral or high performance liquid chromatography 'HPLC' and the formation and crystallization of chiral salts." (Davies Tr. 1473:12-22; JTX-3.10 (9:8-17).)

556. The '638 patent lists three different references that describe general methods that a POSA could use to resolve a compound. (Davies Tr. 1469:16-1470:19; JTX-3.10 (9:17-24.) By acquiring apremilast, the Otezla® drug product, and the '638 patent, Amgen adopted Celgene's statements regarding the content and scope of prior art to the '638 patent, which includes statements regarding the content and scope of the '358 patent. *See Pfizer Inc. v. Teva Pharms. USA, Inc.*, 2006 WL 3041102, at *5 (D.N.J. Oct. 26, 2006) ("Pfizer cannot use the expert affidavits to support its European patent application and then deny that its accepts the truth of the information contained therein. Accordingly, Pfizer's motion to preclude the expert reports on hearsay grounds will be denied.").

557. The inventors of the '638 patent signed an oath affirming the statements in the file history. (Davies Tr. 1461:5-1462:13, 1463:19-1464:13; JTX-16.58-59.) Statements and actions of the assigning patentee before a patent office are binding admissions upon the assignee.

Sherwin-Williams Co. v. PPG Indus., Inc., 2021 WL 211497, at *2-3 & n.3 (W.D. Pa. Jan. 21, 2021) (Sherwin-Williams bound by the "Valspar admissions" during prosecution where it was "undisputed that Sherwin [was] Valspar's successor-in-interest."). A patent owner cannot avoid the consequences of the previous owner's statements simply because they were not an owner at the time the statements were made. *Eastman Kodak Co. v. Goodyear Tire & Rubber Co.*, 114 F.3d 1547, 1559 (Fed. Cir. 1997) ("Zimmer's actions prior to the assignment of the patent rights are imputed to Eastman. A patentee cannot avoid the consequences of his laches by transferring the patent."). The inventors of the '638 patent did not file a patent application with claims directed to an inventive method of separating the enantiomers. (Davies Tr. 1473:23-1474:9.)

558. Dr. Davies testified that the disclosure in the '358 patent regarding separation of the isomers of Formula I compounds was merely a "general statement about any racemate." (Davies Tr. 1408:8-12.)

E. Claim 31 Of The '283 Patent Render The '638 Patent Claims Obvious.

559. Claim 31 of the '283 patent and claims 3 and 6 of the '638 patent both state pharmaceutical compositions of stereomerically pure apremilast suitable for oral administration. The '638 and '283 patents were both assigned by the named inventors to Celgene, which subsequently assigned both patents to Amgen. (Gribble Tr. 615:20-616:9; DDX2-56; JTX-6.1, 66-67 (59:20-45, 61:1-3); JTX-3.1, 21 (31:27-40, 32:9-12).)

560. Claim 31 of the '283 patent and claims 3 and 6 of the '638 patent state overlapping dosage ranges for stereomerically pure apremilast, namely 1 mg to 200 mg (claim 31) and 10 mg to 200 mg (claim 6). (Gribble Tr. 615:20-616:9; DDX2-56; JTX-6.67 (59:20-45, 61:1-3); JTX-3.21 (31:27-40, 32:9-12).)

561. The only difference between claim 31 of the '283 patent and claims 3 and 6 of the '638 patent is that claim 31 describes a crystalline form of apremilast whereas claims 3 and 6 do not specify the crystalline form. (Gribble Tr. 616:10-13.)

562. A POSA would understand claim 31 of the '283 patent to be within the scope of claims 3 and 6 of the '638 patent. (Gribble Tr. 616:14-16; DDX2-56.)

V. The Asserted Claim Of The '536 Patent Is Invalid.

700. Claim 6 of the '536 patent is directed to a method of treating psoriasis using stereomerically pure apremilast. (Davies Tr. 110:24-111:8, 1392:23-1393:10.)

701. Dr. Davies did not consider whether there are any novel aspects in claims 3 and 6 except for apremilast. Dr. Davies did not express an opinion about whether there was anything new of novel about the pharmaceutical composition of the '638 patent beyond the inclusion of apremilast. (*Id.* at 1394:25-1395:13.)

A. The Person of Ordinary Skill in the Art For The '536 Patent.

702. A POSA for the '536 patent would have been a scientist with a Ph.D. in a field such as pharmacology, with one or two years of experience in research and development of pharmaceutical compounds, or would have had a Master's or similar degree, as well as three or more years of experience in research and development of pharmaceutical compounds. (Page Tr. 697:21-698:4; DDX3-6.)

703. Further, the POSA would be part of a team involved in the discovery and development of a new drug and typically include medicinal chemists, pharmacologists, toxicologists, formulation and scale up scientists, regulatory affairs specialists, clinicians with relevant experience in the treatment of therapeutic areas under consideration, and persons with commercial/marketing expertise. (Page Tr. 698:5-11; DDX3-6.)

704. Amgen proposed an alternative definition of a POSA that does not afford enough education or experience to a POSA. (Knowles Tr. 200:10-23; PDX4-4.)

705. Were Defendants' expert Dr. Page to apply Amgen's expert Dr. Knowles's definition of a POSA, Dr. Page's opinions would not change. (Page Tr. 698:24-699:2; DDX3-7.)

706. Defendants' definition of a POSA is the correct definition of a POSA as it stays true to the subject matter of the '536 patent, which is generally directed to the administration of stereomerically pure apremilast for the treatment of psoriasis. (*See, e.g.*, JTX-7.20-21 (30:64-31:3 (claim 1), 31:14-16 (claim 6)).)

B. The '536 Patent Priority Date is March 20, 2002.

707. Both Amgen and Defendants' experts used a priority date of March 20 2002 for the '536 patent, which is the effective filing date of Provisional Application No. 60/366,515. (Page Tr. 699:5-11; Gilmore Tr. 866:16-18; Alexis Tr. 1746:5-8.)

C. Technical Background

708. Defendants' statements above on the Scope and Content of the Prior Art are incorporated here by reference. (DFF ¶¶ 200-99.)

1. Apremilast

709. Indeed, in 2000, the '358 patent (assigned to Celgene) claimed the use of certain compounds, including thalidomide analogues, for inhibiting PDE4, thereby increasing cAMP levels and decreasing production of TNF-α, which "constitute valuable therapeutic strategies for the treatment of many inflammatory, infectious, immunological or malignant diseases," including psoriasis and rheumatoid arthritis. (DTX-174.3-4 (1:5-11, 4:35-48).) Apremilast was specifically disclosed in the '358 patent in its racemic form as one of the compounds of "Formula I," which are disclosed as selective PDE4 inhibitors that decrease the levels of TNF-α

and are therapeutically useful for treating immune and inflammatory conditions. (DTX-174.4, 9 (4:35-48, 14:34-55 (Example 12)).)

2. Psoriasis

710. Psoriasis is a chronic skin condition that affects about 1% to 3% of the total U.S. population. (DTX-215.1; DTX-217.1; JTX-67.12.) Although not usually life-threatening, psoriasis is a disabling disease that can cause significant morbidity, and currently has no cure. (DTX-215.1; DTX-217.1; JTX-67.12; Gilmore Tr. 820:21-24; DDX-4.7.)

711. Psoriasis is typically characterized by "defects in the normal cycle of epidermal development that lead to epidermal hyperproliferation, altered maturation of the skin, inflammation, and vascular alterations." (DTX-215.1.) These characteristics often physically manifest as "areas of dry, thickened, scaling, silvery white and reddened skin" that "may hurt, itch, and bleed." (*Id.*) The extent of psoriasis in a patient "can range from a few small plaques to generalized lesions," which "may be located almost anywhere on the body." (*Id.*) "The most common form [of psoriasis] is plaque psoriasis, occurring in about 90% of patients." (*Id.* at 3.) "In this type of psoriasis, lesions start as small papules that grow and unite to form plaques" and "have the classic silvery white, scaly appearance." (*Id.*) In addition, psoriasis can be cyclical—some patients exhibit symptoms and then go into remission for various periods of time, whereas others consistently have active lesions. (*Id.* at 1.) Up to 20% of patients with psoriasis develop psoriatic arthritis, an inflammatory arthritis condition, with symptoms very similar to rheumatoid arthritis. (*Id.* at 4; JTX-67.12; Gilmore Tr. 822:10-12.)

712. The severity of psoriasis is usually determined by using the Psoriasis Area and Severity Index ("PASI"). (DTX-217.1; Gilmore Tr. 822:13-18; DDX-4.8.) This index "takes into account the size of the area involved, redness, thickness, and scaling." (DTX-217.1; Gilmore Tr. 822:23-823:4; DDX-4.8.) Patients with mild psoriasis have a score of less than 10,

those with moderate disease have a score of 10 to 50, and severe psoriasis is defined by a score of greater than 50 (with a maximal score of 72). (DTX-217.1; Gilmore Tr. 823:5-16; DDX-4.8.)

713. Although the primary cause of psoriasis remains unknown, "[b]iochemical studies have recognized specific changes in the expression of many cellular markers in psoriasis." (DTX-215.2; *see also* JTX-67.12 ("The exact cause of psoriasis is unknown, although it appears to be an autoimmune disease with a likelihood for genetic predisposition.").) These biochemical markers include (among others), changing levels of immunomodulating cytokines, such as interleukin-1 ("IL-1"), IL-6, IL-8, and tumor necrosis factor ("TNF"). (DTX-215.2; *see also* JTX-67.12 ("There is a large T-cell infiltration in the affected regions of the skin, with CD4+ lymphocytes in the dermis and CD8+ lymphocytes in the epidermis. These lymphocytes secrete IL-2, IFN-γ and TNF-α which alter keratinocyte proliferation and differentiation.").)

714. Indeed, "it has been shown that the overheated inflammatory cytokine network is involved in psoriatic inflammation." (DTX-140.2) More specifically, "[a]t exacerbation, psoriatic patients express generalized inflammatory reactions including fever, joint pain, leukocytosis and acute phase protein induction. These findings strongly suggest the involvement of inflammatory cytokines as mediators." (*Id.*) It was also well known prior to 2002 that the expression of TNF, a proinflammatory cytokine, is elevated in patients with psoriasis. (DTX-215.2.)

715. Moreover, there are a number of factors that are believed to increase the risk of developing psoriasis. For example, studies have shown that psoriasis may be "a genetically linked disease and may be carried on more than one gene." (*Id.* at 4.) Indeed, about 30% of patients with psoriasis have reported a family history of the disease. (*Id.*) Psoriasis can also be triggered by many non-genetic factors, such as mechanical, ultraviolet, and chemical injury,

various infections (e.g., streptococcal infections and HIV), prescription drug use, psychological stress, endocrine and hormonal changes, obesity, alcohol, and smoking. (*Id.*)

716. Psoriasis is considered to be an autoimmune skin disease and an inflammatory disease because of the excessive release of the inflammatory mediator tumor necrosis factor-α ("TNF-α"). (Page Tr. 705:7-19; DTX-140.1; JTX-67.12; DDX3-14.)

717. Measurement of the levels of TNF-α produced by peripheral blood monocytes ("PBMC") obtained from psoriasis patients showed that TNF-α produced by these cells is significantly higher compared to the levels produced by PBMC obtained from healthy subjects. (DTX-140.1; DDX3-14.) Mizutani states that the "results strongly suggest that inflammatory cytokines, especially TNF-α, from monocytes are involved in the pathogenesis of psoriasis." (*Id.*) This provided a POSA with motivation to reduce levels of TNF-α in a person with psoriasis, to contribute to an anti-inflammatory effect. (Page Tr. 705:7-19; DTX-140.1; DDX3-14.)

a. Treatment of Psoriasis

718. There is currently no cure for psoriasis, and thus the primary goal of treatment is to "decrease the severity and extent of psoriasis to the point at which it no longer interferes substantially with the patient's occupation, personal or social life, or well-being." (DTX-217.2; Gilmore Tr. 824:23-825:12.) Treatment options differ from patient to patient and with the severity of the disease. (DTX-215.13.) Both as of 2002 and today, topical therapies are generally used as a first line of treatment for patients with stable plaque psoriasis, particularly if the extent of the disease is milder. (DTX-215.13; DTX-217.2-3.) As of 2002, topical treatment options for psoriasis included emollients, keratolytic agents, anthralin, tars, topical corticosteroids, and vitamin D_3 analogues. (DTX-215.5; DTX-217.3-4.)

719. If a patient does not respond adequately to topical therapy, or if the patient's disease is more extensive (i.e., more than 20% of the body is covered in plaques or lesions or if

there is joint involvement), then systemic therapy is usually warranted. (DTX-215.5, 13; DTX-217.2-3.) By 2002, systemic treatments included either photochemotherapy or oral systemic drug therapy, such as with retinoids, methotrexate, or cyclosporine. (DTX-372.2; Gilmore Tr. 827:3-11; DDX-4.11.)

720. ***Phototherapy.*** "Phototherapy has been used to treat various skin disorders for over 100 years and is a key treatment for moderate to severe psoriasis." (DTX-215.12.) The two types of ultraviolet light that have been used for treating dermatologic problems, including psoriasis, are ultraviolet A ("UVA") and ultraviolet B ("UVB"). (*Id.*) UVB phototherapy is typically used in combination with coal tar and is effective within two to three weeks. (DTX-217.5.) Difficulties associated with this therapy include "the time required for exposure to coal tar and ultraviolet B, patients' dislike of the smelly coal-tar preparations, and the expense of the approximately 30 treatments needed to obtain reasonable benefit." (*Id.*)

721. Photochemotherapy combines UVA phototherapy with a photosensitizing drug, such as psoralen (commonly referred to as "PUVA"). (DTX-215.12.) PUVA has shown to be beneficial in treating psoriasis because of its "antiproliferative, anti-inflammatory, and immunosuppressive effects." (*Id.*) However, long-term treatment with PUVA can result in "premature cutaneous aging, cataracts, and skin cancers, including melanoma." (*Id.* at 13.) As such, patients being treated with PUVA "should be monitored on a long-term basis for early signs of melanoma." (*Id.*)

722. ***Retinoids.*** "Retinoids are biological derivatives of vitamin A." (*Id.* at 9.) Retinoids are understood to be therapeutically useful in the treatment of psoriasis because they "stimulate epithelial differentiation and inhibit malignant transformation in skin and mucous membranes." (DTX-217.6.) Prior to 2002, there were two oral retinoids commercially

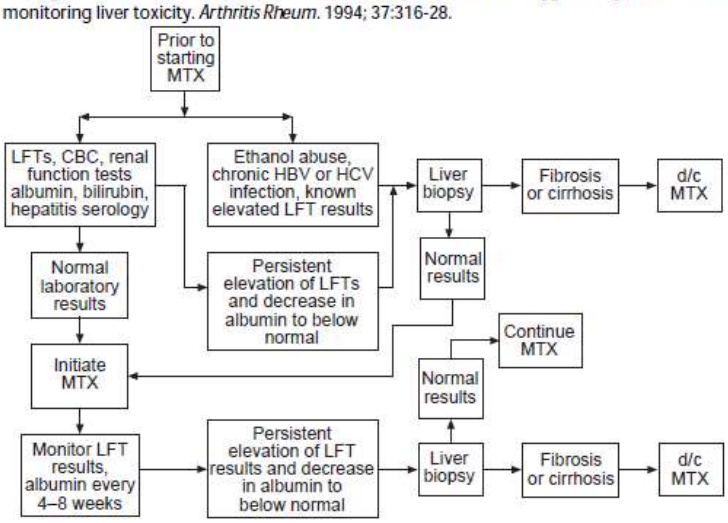
available—etretinate and acitretin (the active metabolite of etretinate), although etretinate was withdrawn from the U.S. market in March 1998 because of its toxicity. (DTX-215.10.) The use of oral retinoids is normally limited to patients with severe forms of psoriasis because the side effects can be serious. (*Id.*) Adverse effects include "peeling and drying skin, diffuse alopecia, nail changes, and sticky or clammy skin," as well as "muscle pain and calcification of ligaments." (*Id.*) Moreover, acitretin "should be avoided in patients with severe diseases of the liver and kidneys and in patients with a history of alcohol abuse." (*Id.*) Studies have shown that alcohol consumption "alter[s] the metabolism of acitretin and may lead to measurable blood levels of etretinate for up to two years." (*Id.*) Thus, patients taking acitretin need to be monitored during treatment "for changes in concentrations of serum lipids, liver enzymes, and serum creatinine." (*Id.*) Acitretin is also contraindicated in pregnancy because of its teratogenic risk. (*Id.*) Women contemplating using acitretin "should use effective contraception one month before treatment begins and for up to two years after it ends." (*Id.*)

723. ***Methotrexate.*** "Methotrexate is a folic acid analogue and antagonist." (*Id.*) Although "[t]he complete mechanism of action in psoriasis is only partially understood," it is believed that "methotrexate affects epidermal cells and various immune-system cell lines." (*Id.*) "Methotrexate is indicated for use in the treatment of moderate to severe psoriasis." (*Id.*) It is typically "reserved for patients who are unresponsive to topical treatment modalities, retinoids, and phototherapy," and who have a severe form of psoriasis, such as "plaque psoriasis involving more than 20% of the body surface." (*Id.*) In addition, methotrexate should only be administered to patients with normal renal and liver function. (DTX-217.5.) This is necessary "because 85% of the drug is excreted through the kidneys, and patients with poor renal function have sustained increases in plasma drug concentrations, leading to acute side effects, including

leukopenia and acute gastrointestinal or cutaneous erosions." (*Id.*) Further, the "chief long-term side effect of methotrexate therapy is cirrhosis; patients with a history of liver disease or excessive alcohol intake and those with abnormal liver function should not receive the drug." (*Id.* at 6.)

724. As such, patients taking methotrexate need to be consistently monitored for potential liver damage. (DTX-215.11; Gilmore Tr. 938:18-21.) "Retrospective studies have indicated that cirrhosis develops in approximately 3 percent of patients with psoriasis in whom the cumulative dose of methotrexate is 1.5 g or less, with the fraction increasing to 20 to 25 percent among patients who have received 4 g." (DTX-217.6.) Thus, "[t]raditional guidelines suggested that cumulative dose [of methotrexate] was predictive of hepatotoxicity." (DTX-215.11.) Under these guidelines, "[c]linicians would calculate the cumulative dose and, if it exceeded 1.5 g, perform a liver biopsy whether liver function test results were normal or not." (*Id.*) The American College of Rheumatology guidelines for monitoring methotrexate therapy, reproduced below, recommend conducting liver function tests before initiating therapy and at regular intervals thereafter, and performing a liver biopsy if necessary. (*Id.* (Figure 14).)

Figure 14. American College of Rheumatology algorithm for managing methotrexate (MTX)-induced liver damage. LFTs = liver function tests, CBC = complete blood count, HBV = hepatitis B virus, HCV = hepatitis C virus, d/c = discontinue. Adapted from Kremer JM, Alarcon GS, Lightfoot RWJ et al. Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. *Arthritis Rheum.* 1994; 37:316-28.



725. Another adverse effect associated with methotrexate is osteopathy. (*Id.*) "Methotrexate-induced osteopathy is indicated by bone pain, radiologic findings of osteoporosis, and stress fractures localized to the distal tibias." (*Id.*) Thus, "[b]lood counts should be performed routinely in methotrexate recipients to check for anemia, leukopenia, and thrombocytopenia." (*Id.*) Methotrexate is also contraindicated in "pregnant patients; lactating mothers; individuals who are trying to conceive; patients with severe anemia, leukopenia, or thrombocytopenia; … and patients with active infectious diseases in whom a compromise in immune function could result in worsening of the disease." (*Id.* at 10-11.)

726. ***Cyclosporine.*** As of 2002, there was an "increasing interest in using cyclosporine to treat psoriasis because of outstanding improvements seen with it and because of this agent's immunomodulating properties." (*Id.* at 11.) As with other medications that are used for treating psoriasis, "the usefulness of cyclosporine for psoriasis was found serendipitously when it was used to treat another condition." (*Id.*) Studies have shown that oral cyclosporine is "effective in the treatment of psoriatic lesions resistant to other therapies." (*Id.* at 11-12.) Indeed, "[p]atients with extensive psoriasis who are treated with cyclosporine for two weeks or more improve rapidly. However, like other treatments for psoriasis, cyclosporine is not curative, and the disease relapses within days or weeks after the discontinuation of treatment." (DTX-217.6.) Adverse effects include "hypertension and impairment of renal function, which may be irreversible." (*Id.* at 7.)

727. Thus, prior to 2002, there were a number of conventional topical and systemic therapies available for the treatment of psoriasis. (Gilmore Tr. 827:3-11; DDX-4.11.) However, for the reasons discussed above, each of these therapies had its own advantages and disadvantages.

3. PDE4 Inhibitors

728. There are multiple families of phosphodiesterases ("PDEs"), enzymes that regulate the levels of the intracellular signaling molecule cyclic adenosine monophosphate ("cAMP"). (Page Tr. 700:11-14, 701:10-18; DTX-174.4 (4:12-17); DDX3-10.) PDE enzymes are responsible for the inactivation of cAMP. (DTX-174.4 (4:12-14); DDX3-10.) It has long been appreciated that non-selective inhibitors of PDEs (such as theophylline) could have clinical benefit in a number of diseases. (Page Tr. 700:15-21; DDX3-9.) However, it was also recognized that by inhibiting these PDEs non-selectively, there were also a number of unwanted side effects as these PDEs were found in many cell types beyond those targeted to obtain clinical benefit. (Page Tr. 700:15-701:4; DDX3-10.)

729. The recognition by the end of the 1980s that there was cellular and tissue selectivity of where particular PDEs were located provided the logic and the motivation to find drugs that were selective inhibitors for particular PDEs that could have clinical benefit. (Page Tr. 700:22-701:4; DDX3-9.)

a. Inhibiting the PDE4 Enzyme to Reduce TNFα Production.

730. As of 2002, a POSA would have known that PDE4 inhibitors were useful in the treatment of inflammatory conditions and diseases, including psoriasis, by decreasing the production of certain pro-inflammatory proteins, more specifically TNF-α. (DTX-174.4 (4:35-53); JTX-67.12; Page Tr. 700:22-701:18; DDX3-11.)

731. PDE4, in particular, regulates the level of cAMP inside different inflammatory cells and thereby controls the function of the cell under normal physiological conditions, including the release of TNF-α. (Page Tr. 701:10-18; DDX3-10.)

732. TNF-α is a cell-signaling protein (otherwise known as a cytokine) that is released by inflammatory cells during an immune response. (DTX-174.3 (1:15-17); *see also* Knowles Tr.

238:10-11 (TNF-α is a proinflammatory cytokine).) When administered to humans, TNF-α "causes inflammation, fever, cardiovascular effects, hemorrhage, coagulation, and acute phase responses similar to those seen during acute infections and shock states." (DTX-174.3 (1:17-21).) Thus, "[e]xcessive or unregulated TNF[-]α production … has been implicated in a number of disease conditions," including endotoxemia and/or toxic shock syndrome, rheumatoid arthritis, Crohn's disease, inflammatory bowel disease, cachexia, and Adult Respiratory Distress Syndrome. (*Id.* (1:21-30); *see also* JTX-69.1 ("Excessive TNF-α levels have been found to be associated with a number of inflammatory and autoimmune conditions including rheumatoid arthritis."); JTX-68.1 ("TNF-α is a key cytokine in the inflammatory cascade and elevated TNF-α levels are associated with inflammatory diseases."); JTX-66.3 ("TNF-α is a key regulator of other pro-inflammatory cytokines and leukocyte adhesion molecules and therefore represents a therapeutic target in a number of conditions where the overproduction of TNF-α is associated with a pathological inflammatory cascade.").) It was further known that increased levels of TNF-α are implicated in the pathogenesis of psoriasis. (*See, e.g.*, DTX-215.2; DTX-140.1; Page Tr. 705:10-22.)

733. As such, the "control of TNF-α levels could be a key to the treatment of a wide range of [inflammatory] diseases," including psoriasis. (JTX-69.1; Page Tr. 705:10-22.) For example, the direct inhibition of TNF-α activity "with monoclonal anti-TNF[-]α antibodies has been shown to be beneficial in rheumatoid arthritis." (DTX-174.3 (2:35-36); *see also* JTX-69.1 ("The validity of this approach has recently been demonstrated by the clinical benefit observed in the treatment of rheumatoid arthritis and Crohn's disease by TNF-α antibodies and TNF-α soluble receptors."); JTX-68.1 ("Recent successful clinical trials in rheumatoid arthritis and inflammatory bowel disease with TNF-α antibodies and soluble TNF-α receptors have validated

the inhibition of TNF-α as a clinical treatment.").) Indeed, Enbrel, an anti-TNF-α biological agent, was FDA-approved for the treatment of rheumatoid arthritis before 2002. (JTX-66.3; Gilmore Tr. 828:10-11.)

734. TNF-α production can also be indirectly inhibited by increasing the levels ofcAMP. cAMP is a "second messenger[] that mediate[s] biological responses to a variety of hormones, neurotransmitters, autocoids and drugs." (JTX-67.1.) The "elevation of cAMP in inflammatory leukocytes inhibits their activation and the subsequent release of inflammatory mediators, including TNF[-]α." (DTX-174.4 (4:3-6).) cAMP levels, in turn, are primarily controlled by PDEs, which break down and inactivate cAMP. (*Id.* (4:12-14); *see also* JTX-68.2.) "There are seven known members of the family of PDEs," (DTX-174.4 (4:16-17)), with PDE4 being the "major" enzyme present in inflammatory cells that produce TNF-α. (JTX-68.2.) Thus, PDE4 inhibition "is particularly effective in … the inhibition of inflammatory mediator release," including the release of TNF-α cytokines. (DTX-174.4 (4:17-19); JTX-68.2; *see also* JTX-137.1 ("Recent data have shown that PDE4 inhibitors potently suppress TNF[-]α-release from mononuclear phagocytes.").)

735. In particular, the "[i]nhibition of PDE4 results in an elevation of cAMP in [inflammatory] cells, which in turn downregulates the inflammatory response" caused by the overproduction of TNF-α. (JTX-67.1; *see also* DTX-174.4 (4:23-25) ("Thus, compounds that inhibit PDE IV specifically, would exhibit the desirable inhibition of inflammation."); JTX-137.12 ("Phosphodiesterase 4 inhibitors, by increasing intracellular cAMP levels, lead to the inhibition of inflammatory cell activation.").) "These observations opened the possibility of using PDE4 inhibitors in the treatment of pathologies associated with over expression and production of TNF[-]α, such as certain auto-immune diseases." (JTX-137.1; *see also* JTX-67.1

("The potential use of PDE4 inhibitors as anti-inflammatory agents for the treatment of asthma and other inflammatory disorders has received considerable attention from the pharmaceutical industry.").) "Decreasing TNF[-]α levels, increasing cAMP levels, and inhibiting PDE IV thus constitute valuable therapeutic strategies for the treatment of many inflammatory, infectious, immunological or malignant diseases," including psoriasis. (DTX-174.4 (4:35-48).)

736. In an inflammatory cell under normal physiological conditions, when a cell receives input of stimuli, levels of cAMP rise in the cell, which regulates the extent to which the inflammatory mediator TNF-α is released. (Page Tr. 703:9-704:6; DDX3-12.) PDE4 would also break down cAMP to an inactive substance (called AMP). (Page Tr. 703:9-23; DDX3-12.)

737. When an inflammatory cell is exposed to a PDE4 inhibitor, PDE4 is inhibited, which causes levels of cAMP to rise, which results in greater inhibition of the release of TNF-α from that cell. (Page Tr. 701:20-25, 703:9-704:6; DDX3-12.)

738. PDE4 is the predominant isoenzyme expressed in the majority of inflammatory cells that have been implicated in the pathogenesis of inflammatory diseases, including psoriasis, such as lymphocytes and monocytes. (Page Tr. 701:5-9; DDX3-10.)

b. PDE4 Inhibitors in the Treatment of Inflammatory Conditions, Including Psoriasis.

739. As of the priority date, these observations led to a number of pharmaceutical companies discovering and developing selective PDE4 inhibitors as possible treatments for a range of diseases, including inflammatory diseases, as inhibiting PDE4 in these inflammatory cells caused profound inhibition of the function of these cells. (Page Tr. 704:8-22; DDX3-13.)

740. In the 1980s and 1990s, orally active selective PDE4 inhibitors were identified, such as CDP840, cilomilast (Ariflo), and roflumilast () for the treatment of inflammatory

diseases. (JTX-67.1; JTX-67.5 (Table 2); JTX-142.4-5; PDX4-12; *see also* Knowles Tr. 1669:5-6 (noting that Ariflo is another name for cilomilast).)

741. There are many observations in the literature reporting that selective PDE4 inhibitors have broad anti-inflammatory activity that is recognized in various reviews. (*See, e.g.*, JTX-137.1 (stating that the PDE4 family "represents a molecular target for new antiasthmatic and anti-inflammatory drugs" and that "PDE4 is the predominant form of PDE found in cell-types implicated in chronic inflammatory diseases").) It has also long been recognized that selective PDE4 inhibitors can suppress the release of a range of inflammatory mediators from inflammatory cells. (*See, e.g.*, JTX-137.12 ("Phosphodiesterase 4 inhibitors, by increasing intracellular cAMP levels, lead to the inhibition of inflammatory cell activation."). These effects provided a strong scientific rationale for the development of selective, orally active PDE4 inhibitors as novel treatments for a wide range of inflammatory diseases. (Page Tr. 704:8-22; DDX3-13; *see also* JTX-137.1 (disclosing that PDE4 inhibitors may be used "in the treatment of pathologies associated with over expression and production of TNFα, such as certain auto-immune diseases" and that "[t]he PDE4 family which represents a molecular target for new antiasthmatic and anti-inflammatory drugs has attracted much interest").)

742. In 1999, the PDE4 inhibitor roflumilast was in phase 2 and 3 clinical studies in humans for the treatment of chronic obstructive pulmonary disease ("COPD") and asthma. (JTX-142.4-5; PDX4-12.)

743. In 1999, the PDE4 inhibitor cilomilast was in phase 3 clinical trials in humans for the treatment of COPD and asthma. (JTX-142.4; JTX-67.5; PDX4-12.)

744. As of 2002, PDE4 inhibitors had been shown to ameliorate disease progression in animal models of rheumatoid arthritis. There was "considerable evidence … that the pro-

inflammatory cytokines such as IL-1β, IL-6 and TNF-α are the major contributors to joint tissue damage, inflammation, hyperplasia, pannus formation and bone resorption" in rheumatoid arthritis. (JTX-67.9.) "The impressive *in vitro* anti-inflammatory profile of PDE4 inhibitors and their utility in the modulation of TNF-α *in vivo* prompted a number of groups to explore the potential of PDE4 inhibitors in animal models of [rheumatoid arthritis]." (*Id.* at 10.) These studies showed that administration of a PDE4 inhibitor significantly ameliorated the progression of disease by improving joint destruction, synovitis, and fibrosis. (*Id.*; *see also* JTX-137.12 ("In a model of collagen II-induced arthritis in rats, very similar to human rheumatoid arthritis, rolipram [a PDE4 inhibitor] given subcutaneously 2 mg/kg twice daily for five days before the onset of arthritis significantly delayed the appearance of the symptoms.").)

745. In clinical studies, the first selective PDE4 inhibitor to be studied in rheumatoid arthritis patients was called RP73401. (JTX-67.10.) "In a small placebo-controlled, double-blind Phase II study of 35 RA patients, RP73401 (400 µg t.i.d.) was able to induce a positive trend towards clinical improvement … with no serious or unexpected adverse events." (JTX-67.10.) Although the results from this study were not statistically significant, "this was probably due to the size of the study and its short duration." (*Id.*)

746. It was well established that TNF-α levels are overexpressed in patients with psoriasis (Page Tr. 705:10-22; DTX-140.1; DDX3-14), and that up to 20% of psoriasis patients develop psoriatic arthritis, "with symptoms that are very similar to [rheumatoid arthritis]." (JTX-67.12; DTX-215.4.) "Thus, the potential utility of PDE4 inhibitors in RA and the broad spectrum anti-inflammatory action of such compounds suggest that they have the potential to provide a beneficial treatment for psoriasis." (JTX-67.12.) Prior to 2002, a "number of groups ha[d] investigated the effect of PDE4 inhibitors on skin." (*Id.*) The results showed that

"treatment of epidermal basal cells, in primary culture, with the PDE4 inhibitor, Ro20-1724, leads to a three[-] fold increase in cAMP concentrations, illustrating that these cells contain active PDE4 protein." (*Id.*) Another "similar study comparing the effects of Ro20-1724 on psoriatic epidermal slices and keratomed psoriatic epidermal slices showed a very marked elevation of cAMP over controls (1395% increase in cAMP in keratomed psoriatic epidermis), suggesting that PDE4 inhibitors may be potentially beneficial in psoriasis." (*Id.*) With respect to the "inflammatory component of the disease, PDE4 inhibitors have been shown to inhibit the inflammatory response of a number of mediators *via* either topical or systemic administration." (*Id.*)

747. In the context of psoriasis, therefore, it is noteworthy that PDE4 inhibitors have been shown to inhibit production of pro-inflammatory cytokines, such as TNF-α, IFN-γ and IL-2 from peripheral blood monocytes and T cells. (*See, e.g.*, JTX-67.5.) PDE4 enzymes were also known to be expressed in the majority of inflammatory cells (e.g., lymphocytes and monocytes) that have been implicated in a number of inflammatory diseases, such as psoriasis. (Page Tr. 701:5-9; DDX3-10.)

748. Indeed, in the clinic, the selective PDE4 inhibitor Ro20-1724 was investigated in two double-blind studies comparing its effectiveness to vehicle when administered topically to patients with psoriasis. (Page Tr. 712:20-713:4; JTX-67.12; DDX3-23.) In these studies, the PDE4 inhibitor was shown to improve psoriatic lesions, and it "had no adverse systemic or cutaneous effects, suggesting the therapeutic potential of such compounds in the treatment of psoriasis." (Page Tr. 712:20-713:4; JTX-67.12; DDX3-23.)

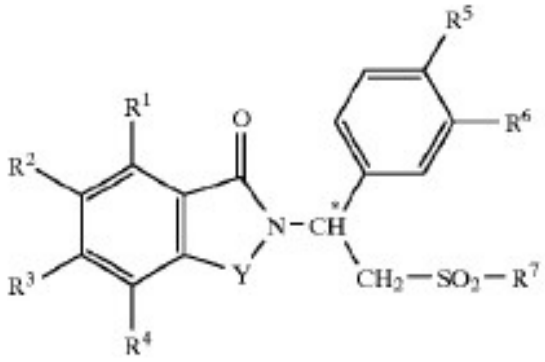
4. Prior Art

a. The ’358 Patent

749. Defendants’ statements above on the ’358 patent are incorporated here. (DFF ¶¶ 271-99.)

750. In 2000, apremilast was disclosed and claimed in the ’358 patent, which was issued to Celgene and which names the same inventors as those listed on the ’536 patent. (DTX-174.9 (14:34-55 (Example 12)).) The ’358 patent discloses compounds of the Formula I (reproduced below), and their use in inhibiting phosphodiesterases, particularly PDE4, and in the treatment of diseases mediated by inhibition of PDE4. (*Id.* at 3-5 (1:5-11, 4:28-31, 5:1-13).)

I



751. The ’358 patent discloses that “the carbon atom designated * constitutes a center of chirality;” Y can be C=O; R^1, R^2, and R^3 can each be a hydrogen; R^4 can be $–NR^8R^9$ where each of R^8 and R^9, taken independently of the other, can be a hydrogen and the other is $–COR^{10}$ where R^{10} is an alkyl of 1 to 8 carbons; R^5 and R^6, independently of the other, can be an alkoxy of 1 to 4 carbon atoms; and R^7 can be an alkyl of 1 to 8 carbons. (*Id.* at 4, 12 (4:66-6:67, 20:15-65 (claim 1)).)

752. Specifically, the ’358 patent teaches that “[t]umor necrosis factor α, or TNF[-]α, is a cytokine which is released primarily by mononuclear phagocytes in response to a number of

immunostimulators." (*Id.* at 3 (1:15-17); Page Tr. 706:10-21; DDX3-16.) When TNF-α is "administered to animals or humans, it causes inflammation, fever, cardiovascular effects, hemorrhage, coagulation, and acute phase responses similar to those seen during acute infections and shock states." (DTX-174.3 (1:17-21).) "Excessive or unregulated TNF[-]α production thus has been implicated in a number of disease conditions," including "endotoxemia and/or toxic shock syndrome; rheumatoid arthritis, Crohn's disease, [inflammatory bowel disease], cachexia and Adult Respiratory Distress Syndrome." (DTX-174.3 (1:21-31) (internal citations omitted); Page Tr. 706:10-21; DDX3-16.) As such, "TNF[-]α blockage with monoclonal anti-TNF[-]α antibodies has been shown to be beneficial" in numerous diseases, including rheumatoid arthritis. (DTX-174.3 (2:35-39); Page Tr. 706:10-18.) The '358 patent also discloses that the compounds described therein decrease the levels of TNF-α. (DTX-174.4 (4:57-63); Page Tr. 706:24-707:7; DDX-3-17.)

753. The '358 patent also discloses "the method of reducing levels of [TNF-α] and treating inflammatory and autoimmune diseases in a mammal through the administration" of the claimed compounds. (DTX-174.3 (1:7-9); Page Tr. 706:10-18; DDX-3-16.)

754. In addition, the '358 patent discloses that "[m]any cellular functions are mediated by levels of [cAMP]. Such cellular functions can contribute to inflammatory conditions and diseases including asthma, inflammation, and other conditions." (DTX-174.4 (3:66-4:3).) In particular, "[i]t has been shown that the elevation of cAMP in inflammatory leukocytes inhibits their activation and the subsequent release of inflammatory mediators, including TNF[-]α." (*Id.* (4:3-6); Page Tr. 706:24-707:7; DDX3-17.) The '358 patent provides that "[t]he primary cellular mechanism for the inactivation of cAMP is the breakdown of cAMP by a family of isoenzymes referred to as cyclic nucleotide phosphodiesterases (PDE)." (DTX-174.4 (4:12-14).) "There are

seven known members of the family of PDEs," (*Id.* (4:16-17)), and "[i]t is recognized … that the inhibition of PDE type IV is particularly effective in both the inhibition of inflammatory mediator release and the relaxation of airway smooth muscle." (*Id.* (4:17-20); Page Tr. 707:12-24; DDX3-18.)

755. As such, "compounds that inhibit PDE IV specifically, would exhibit the desirable inhibition of inflammation and relaxation of airway smooth muscle with a minimum of unwanted side effects, such as cardiovascular or anti-platelet effects." (DTX-174.4 (4:23-27); Page Tr. 707:12-24; DDX3-18.) However, "[c]urrently used PDE IV inhibitors lack the selective action at acceptable therapeutic doses." (DTX-174.4 (4:27-28); Page Tr. 707:12-24; DDX3-18.) The '358 patent states that "[t]he compounds of the present invention are useful in the inhibition of phosphodiesterases, particularly PDE III and PDE IV, and in the treatment of disease states mediated thereby." (DTX-174.4 (4:28-31).)

756. The '358 patent teaches that "[d]ecreasing TNF[-]α levels, increasing cAMP levels, and inhibiting PDE IV thus constitute valuable therapeutic strategies for the treatment of many inflammatory, infectious, immunological or malignant diseases," including psoriasis. (*Id.* (4:35-48); Page Tr. 708:2-11; DDX3-19.) More specifically, the '358 patent provides that "[t]he compounds of Formula I are used, under the supervision of qualified professionals, to inhibit the undesirable effects of TNF[-]α and PDE IV." (DTX-174.5 (7:1-3); Page Tr. 708:2-11; DDX3-19.)

757. In Example 12, the '358 patent discloses "2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetamidoisoindoline-1,3-dione" and a method of preparing it. (DTX-174.9 (14:34-55).) The racemate "2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetamidoisoindoline-1,3-dione" contains a mixture of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-

methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione ("apremilast") and (-)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. (DFF ¶¶ 418-26.)

758. The '358 patent discloses stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, that is, stereomerically pure apremilast. (*Id.* at ¶¶ 416-74.)

759. The '358 patent also discloses that the compounds of Formula I "can be administered orally, rectally, or parenterally, alone or in combination with other therapeutic agents including antibiotics, steroids, etc., to a mammal in need of treatment." (DTX-174.6 (7:3-6); Page Tr. 708:12-20, 709:11-20.) "The compositions preferably are formulated in unit dosage form, meaning physically discrete units suitable as a unitary dosage, or a predetermined fraction of a unitary dose to be administered in a single or multiple dosage regimen to human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with a suitable pharmaceutical excipient." (DTX-174.7 (9:53-60); Gilmore Tr. 869:25-870:4.) Dr. Gilmore testified that a POSA would understand the '358 patent's teaching that the compositions can "be administered in a single or multiple dosage regimen to human subjects and other mammals" to mean once, twice, or three times daily. (Gilmore Tr. 869:25-870:8.) The '358 patent teaches that "[o]ral dosage forms include tablets, capsules, dragees, and similar shaped, compressed pharmaceutical forms containing from 1 to 100 mg of drug per unit dosage." (DTX-174.7 (9:22-24); Gilmore Tr. 869:14-18, 870:15-18.)

760. The '358 patent also states that "[p]harmaceutical compositions thus comprise one or more compounds of the present invention associated with at least one pharmaceutically

acceptable carrier, diluent or excipient." (DTX-174.7 (9:31-34).) The '358 patent provides that the pharmaceutical compositions "can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders." (*Id.* (9:39-43).)

761. The '358 patent further discloses that compounds of Formula I can be prepared as salts. (*Id.* (9:13-21).) The '358 patent also discloses that the compounds of Formula I can be administered alone or in combination with other therapeutic agents, including antibiotics and steroids. (*Id.* at 6 (7:3-6).)

762. In Examples 22-25, exemplary tablets were prepared containing 100 mg, 75 mg, 10 mg, and 100 mg, respectively, of the active ingredient. (*Id.* at 11-12 (18:7-19:55).)

763. Claim 17 of the '358 patent is directed to a method of reducing undesirable levels of TNF-α in a mammal. (*Id.* at 13 (22:30-32); Page Tr. 709:25-710:15; DDX3-20.)

764. Claim 18 of the '358 patent is directed to a method of inhibiting PDE4 levels in a mammal. (DTX-174.13 (22:33-35); Page Tr. 709:25-710:15; DDX3-20.)

765. Claim 19 of the '358 patent is directed to a pharmaceutical composition of a compound according to claim 1 to reduce levels of TNF-α in a mammal. (DTX-174.13 (22:36-39); Page Tr. 709:25-710:15; DDX3-20.)

766. Though Dr. Knowles opined that a POSA would not have believed the teachings of the '358 patent that all of the compounds disclosed therein were inhibitors of TNF-α (Knowles Tr. 1736:6-1737:6), he acknowledged that statements made in an application to the Patent and Trademark Office must be truthful and claim only that which was actually been invented. (*Id.* at 1733:10-1735:8.) Dr. Knowles also acknowledged that the '358 patent's specification does not

exclude any compound from the disclosed utility as inhibitors of TNF-α and PDE4. (*Id.* at 1735:9-1737:1.)

767. A POSA reading the '358 patent would understand that it describes molecules that are PDE4 inhibitors that can reduce undesirable levels of TNF-α. (Page Tr. 709:25-710:15; DTX-174.13 (22:33-39); DDX3-20.)

768. The '358 patent discloses compounds that are used for inhibiting PDE4 and inhibiting TNF-α and in treating diseases that are mediated by PDE4, such as psoriasis. (Page Tr. 722:15-21; DTX-174.13 (22:33-39); DDX-3-32.)

769. A POSA reading the '358 patent would recognize a method of treating psoriasis with the disclosed compounds, including administering to a patient having psoriasis stereomerically pure apremilast. (Page Tr. 722:15-723:11; DDX3-32.)

b. Dyke 1999

770. Hazel Dyke & John Montana, *The Therapeutic Potential of PDE4 Inhibitors*, 8 EXPERT OPINION INVESTIGATIONAL DRUGS 1301 (1999) ("Dyke 1999"), is an article that was published in 1999. (JTX-67.1; Page Tr. 710:21-711:8; DDX3-21.)

771. Dyke 1999 provides a review of the therapeutic potential of selective PDE4 inhibitors in a variety of diseases. (JTX-67.1; Page Tr. 710:21-711:2; DDX3-21.)

772. Dyke 1999 teaches that "cAMP and cGMP are ubiquitous second messengers that mediate biological responses to a variety of hormones, neurotransmitters, autocoids and drugs." (JTX-67.1.) "Phosphodiesterase enzymes are responsible for the inactivation of [cAMP] and [cGMP]." (*Id.*; Page Tr. 711:9-16; DDX3-21.) PDE4, in particular, is a "cAMP specific phosphodiesterase expressed in inflammatory cells such as eosinophils." (JTX-67.1) Dyke 1999 discloses that "[i]nhibition of PDE4 results in an elevation of cAMP in these cells, which in turn downregulates the inflammatory response. The anti-inflammatory effects of PDE4 inhibitors

have been well documented both *in vitro* and *in vivo* in a variety of animal models." (*Id.*; Page Tr. 711:9-16; DDX3-21.) As such, "[t]he potential use of PDE4 inhibitors as anti-inflammatory agents for the treatment of asthma and other inflammatory disorders has received considerable attention from the pharmaceutical industry." (JTX-67.1) Dyke 1999 specifically looked at the development of treatment with PDE4 inhibitors in asthma, allergic rhinitis, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis, multiple sclerosis, inflammatory bowel disease, and other inflammatory diseases. (*Id.* at 2-15.)

773. Dyke 1999 discloses the second generation PDE4 inhibitors CDP840 and SB2074990 (Ariflo) as being "identified with reduced side effect liability." (JTX-67.1; Page Tr. 711:9-22; DDX3-21.)

774. Dyke 1999 states that PDE4 "is the predominant PDE found in the inflammatory cells associated with asthma." (JTX-67.5.) Further, the "[i]nhibition of PDE4 results in the elevation of cAMP" and "decrease[s] the release of [TNF-α] from macrophages and monocytes and reduce[s] the production of IL-2, IL-4, IL-5, IL-13 and interferon (IFN)-γ from T-lymphocytes." (*Id.*) Based on known information at the time, "[t]here [was] no doubt that selective PDE4 inhibitors exert potent anti-inflammatory effects *in vitro* and thus should have benefits in the treatment of asthma." (*Id.*) In addition to *in vitro* testing, "there are several reports describing the *in vivo* activity of a variety of selective PDE4 inhibitors in animal models." (*Id.*)

775. Dyke 1999 further discloses a PDE4 inhibitor that was being dosed at 300 mg "to be effective in reducing TNF levels and lymphocyte proliferation." (*Id.* at 8.) The drug "was administered to healthy volunteers in a single escalating dose, randomised, placebo-controlled Phase I study." (*Id.*) The drug was dosed up to 400 mg without any adverse events. (*Id.*)

776. Dyke 1999 also discloses the role of PDE4 in COPD. (*Id.*) Patients with COPD show "increased levels of TNF-α and IL-4." (*Id.*) Inhibition of PDE4 "reduces the release of chemotactic factors and TNF-α and increases IL-10 synthesis." (*Id.* at 9 (internal citations omitted).) A specific PDE4 inhibitor was evaluated in COPD patients. (*Id.*) "In a Phase II trial, treatment with SB207499 15 mg twice a day for six weeks resulted in increases in FEV_1 and forced vital capacity (FVC). Efficacy was also demonstrated in a four week trial, with improvement in FEV1 and other parameters. A six week Phase III study in COPD patients receiving 15 mg twice a day demonstrated improvement in FEV_1." (*Id.* (internal citations omitted).)

777. Dyke 1999 teaches that "[r]heumatoid arthritis (RA) is a crippling autoimmune disease, which affects over 1% of the population." (*Id.*) There are "three major pathological features [that] contribute to progressive joint destruction: inflammation; abnormal cellular and humoral responses; [and] synovial hyperplasia." (*Id.*) Dyke 1999 shows the results of PDE4 inhibitors in the treatment of rheumatoid arthritis and other conditions associated with joint tissue damage and inflammation and states that there is "considerable evidence now that the pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α are the major contributors to joint tissue damage, inflammation, hyperplasia, pannus formation and bone resorption." (*Id.*) "Indeed, the use of monoclonal antibodies to TNF-α has shown significant promise in RA clinical trials." (*Id.*) Furthermore, Dyke 1999 discloses that PDE4 inhibitors were known to "suppress the action of a wide range of inflammatory cells, including basophils, eosinophils, and mast cells." (*Id.*)

778. Dyke 1999 discloses that PDE4 inhibitors "also possess a very broad *in vitro* anti-inflammatory action *via* inhibition of the release of reactive oxygen species, prostaglandins, and inflammatory cytokines such as IL-5, IFN-γ and TNF-α." (*Id.* (internal citations omitted).)

"PDE4 inhibitors also have the potential to address the T-cell component of RA, since they are very effective in inhibiting T-cell proliferation mediated *via* a range of different agents." (*Id.* at 9-10.)

779. Dyke 1999 teaches that "[o]f particular interest to the treatment of RA is the potent inhibition of TNF-α released from stimulated monocytes." (*Id.* at 10.) "This *in vitro* effect translates into animal models of inflammation in which anti-inflammatory effects correlate with suppression of TNF-α accumulation." (*Id.*) "The impressive *in vitro* anti-inflammatory profile of PDE4 inhibitors and their utility in the modulation of TNF-α *in vivo* prompted a number of groups to explore the potential of PDE4 inhibitors in animal models of RA." (*Id.*)

780. Early preclinical work "linked the anti-inflammatory activity of the archetypal, selective PDE4 inhibitor, rolipram, in acute inflammation models with significant effects in a mouse adjuvant arthritis model." (*Id.*) This same compound was also "shown to reduce disease severity in collagen II induced arthritis (CIA), in the mouse after sc. [subcutaneous] or ip. [intraperitoneal] injection." (*Id.*) However, rolipram is associated with "dose-limiting side effects, including nausea and emesis, which severely restricted [its] therapeutic utility." (*Id.* at 1.) Dyke 1999 discloses that "[a] considerable amount of work has been reported in this area from workers at Rhone-Poulenc Rorer (RPR)." (*Id.* at 10.) This group "investigated the effect of selective PDE4 inhibitors in both CIA and streptococcal cell wall-(SCW) induced arthritis." (*Id.*) Various compounds were evaluated in these models, which "generally show[ed] significant amelioration of disease." (*Id.*)

781. Dyke 1999 teaches that "[t]he first selective PDE4 inhibitor to be studied clinically in RA patients was the RPR compound, RP73401." (*Id.*) "In a small placebo-controlled, double-blind Phase II study of 35 RA patients, RP73401 (400 µg t.i.d.) was able to

induce a positive trend towards clinical improvement associated with a reduction in C-reactive protein (CRP) and IL-6 serum levels, with no serious or unexpected adverse events." (*Id.*) Although "[t]he results from this study were not statistically significant," Dyke 1999 provides that "this was probably due to the size of the study and its short duration." (*Id.*)

782. Dyke 1999 also notes the use of PDE4 inhibitors for reducing skin eosinophilia. (*Id.* at 11.) For treatment of atopic dermatitis ("AD"), topical use of a selective PDE4 inhibitor was evaluated. (*Id.*) "When applied bilaterally over eight days, the compound effectively inhibited all of the inflammation parameters tested and showed both qualitative and quantitative improvements with no adverse effects." (*Id.* (internal citations omitted).) Dyke 1999 therefore concludes that "there may be a role for PDE4 inhibitors in the treatment of AD." (*Id.* at 12.)

783. Dyke 1999 discloses psoriasis as an inflammatory condition. (*Id.*; Page Tr. 712:8-15; DDX3-22.) In addition, Dyke 1999 provides that "[p]soriasis is a common skin disease affecting approximately 2% of the population." (JTX-67.12.) The disease is "usually recurrent and sometimes very debilitating." (*Id.*) The "exact cause of psoriasis is unknown, although it appears to be an autoimmune disease with a likelihood for genetic predisposition." (*Id.*) Moreover, "[t]here is a large T-cell infiltration in the affected regions of the skin, with CD4+ lymphocytes in the dermis and CD8+ lymphocytes in the epidermis. These lymphocytes secrete IL-2, IFN-γ and TNF-α which alter keratinocyte proliferation and differentiation." (*Id.*; Page Tr. 712:8-15; DDX3-22.) Dyke 1999 discloses that about "5-10% of psoriasis patients develop psoriatic arthritis, with symptoms that are very similar to RA." (JTX-67.12.) As such, "the potential utility of PDE4 inhibitors in RA and the broad-spectrum anti-inflammatory action of such compounds suggests that they have the potential to provide a beneficial treatment for psoriasis." (*Id.*; Page Tr. 712:8-18; DDX3-22.)

784. Dyke 1999 teaches that "a number of groups have investigated the effect of PDE4 inhibitors on skin." (JTX-67.12.) It was shown that "treatment of epidermal basal cells, in primary culture, with the PDE4 inhibitor Ro20-1724, leads to a three[-]fold increase in cAMP concentrations, illustrating that these cells contain active PDE4 protein." (*Id.*) "A similar study comparing the effects of Ro20-1724 on psoriatic epidermal slices and keratomed psoriatic epidermal slices showed a very marked elevation of cAMP over controls (1395% increase in cAMP in keratomed psoriatic epidermis), suggesting that PDE4 inhibitors may be potentially beneficial in psoriasis." (*Id.* (internal citations omitted).) As for "the inflammatory component of the disease, PDE4 inhibitors have been shown to inhibit the inflammatory response of a number of mediators *via* either topical or systemic administration." (*Id.* (internal citations omitted).)

785. In the clinic, topical administration of "[t]he selective PDE4 inhibitor, Ro20-1724, was investigated in two double-blind studies comparing its effectiveness to vehicle." (*Id.*; Page Tr. 712:20-713:4; DDX3-23.) These studies showed that PDE4 inhibition "improve[d] psoriatic lesions" and "had no adverse systemic or cutaneous effects, suggesting the therapeutic potential of such compounds in the treatment of psoriasis." (JTX-67.12; Page Tr. 712:20-713:4; DDX3-23.)

c. Marriott 2001

786. J. Blake Marriott et al., *Immunotherapeutic and Antitumor Potential of Thalidomide Analogues*, 1 EXPERT OPINION BIOLOGICAL THERAPY 675 (2001) ("Marriott 2001"), is an article that was published in 2001. (JTX-66.2; Page Tr. 715:14-716:3; DDX3-26.)

787. Marriott 2001 qualifies as prior art to the '536 patent. (JTX-66.2; Page Tr. 715:14-716:3; DDX3-26.)

788. Marriott 2001 generally discloses the immunotherapeutic and antitumor potential of thalidomide analogues and discloses that thalidomide was "established as an effective immunomodulatory and anti-inflammatory drug" that "show[ed] potential for the treatment of a range of conditions, including rheumatoid arthritis." (JTX-66.2-3; Page Tr. 716:15-20; DDX3-27.) Celgene "initiated a medicinal chemistry program to design and prepare thalidomide analogues," and the "[i]nitial focus of this program was on improving thalidomide's anti-TNF-α properties." (JTX-66.4; Page Tr. 716:4-9; DDX3-26.)

789. Marriott 2001 discloses that "[t]he immunomodulatory drug thalidomide has been shown to be clinically useful in a number of conditions including various immunological disorders and cancers." (JTX-66.2) As of 2001, thalidomide was also described as the World Health Organization's "drug of choice for the treatment of erythema nodosum leprosum," and the FDA approved thalidomide to treat the same condition. (*Id.* at 2-3; Page Tr. 716:23-717:9; DDX3-27.)

790. Thalidomide had also been shown to inhibit synthesis of TNF-α, which is "a key regulator of other pro-inflammatory cytokines and leukocyte adhesion molecules and therefore represents a therapeutic target in a number of conditions where the overproduction of TNF-α is associated with a pathological inflammatory cascade." (JTX-66.3.) "In particular, thalidomide has shown potential for the treatment of a range of conditions, including rheumatoid arthritis (RA), the inflammatory and wasting effects of chronic tuberculosis, Behcet's disease and Crohn's disease." (*Id.* (internal citations omitted).) Its "[c]linical activity *in vivo* is attributed to the wide ranging immunological and non-immunological properties possessed by this drug; these includes anti-TNF-α, T-cell co-stimulatory, anti-angiogenic activities and also direct antitumour activity." (*Id.* at 2.)

791. Marriott 2001 further provides that "[i]n the last few years two anti-TNF-α biological agents have received FDA approval. Enbrel, a TNF-α receptor received approval for the treatment of RA and Infliximab, a TNF-α antibody received approval for Crohn's disease." (*Id.* at 3.) "The success of both of these drugs validated TNF-α blockage as therapeutic treatment." (*Id.*)

792. "However, thalidomide was initially developed as a sedative and its anti-inflammatory and anticancer activities were discovered later." (*Id.* at 4.) As such, Marriott 2001 discloses that "it would seem likely that novel compounds designed using thalidomide structure as a lead would allow optimisation of its immunological and anticancer properties while decreasing its side effects." (*Id.*; Page Tr. 716:4-9; DDX3-26.)

793. "[T]he design of compounds based on the thalidomide structure has led to the synthesis of analogues with greatly enhanced immunological activity and with similarly decreased toxicity." (JTX-66.2.) These analogues "fall into at least two categories: selective cytokine inhibitory drugs (SelCID), which are phosphodiesterase Type 4 (PDE4) inhibitors and immunomodulatory drugs (IMiD)," which "do not inhibit PDE4 and act *via* an unknown mechanism." (*Id.* at 2, 4.)

794. In preclinical studies, the SelCID analogues were shown to be "potent PDE4 inhibitors and this activity appear[ed] to correlate well with TNF-α inhibition." (*Id.* at 4; Page Tr. 717:12-21; DDX3-28.) "Several of these analogues have been reported to show good activity in the inhibition of serum TNF-α levels in LPS [lipopolysaccharide] treated mice." (JTX-66.4; DDX3-28.) Marriott 2001 further discloses that "[t]he development of these compounds is being expanded quickly and should soon lead to full-scale clinical trials." (JTX-66.6; DDX3-29.) More particularly, "[c]linical development of the SelCID compounds have been underway for

the past five years although no clinical data has yet been published." (JTX-66.6; Page Tr. 717:22-718:7; DDX3-29.)

795. "The first SelCID to enter into clinical development was CDC-801," which "is approximately 10-fold more potent a TNF-α inhibitor than thalidomide and was found to be non-teratogenic." (JTX-66.6; Page Tr. 717:22-718:7; Knowles Tr. 1715:7-1716:1.) Marriott 2001 provides that CDC-801 "successfully completed two Phase I clinical trials in the UK," with no serious adverse events reported in the second trial. (JTX-66.6; Page Tr. 717:22-718:18; Knowles Tr. 1718:19-1720:25.) For CDC-801 to get into clinical trials, it would have had to pass through all the necessary preclinical and regulatory safety experiments. (Page Tr. 717:22-718:18.) This would include toxicity studies that occurred over a chronic period of treatment, which would help determine the dose that would be allowed to be used in man for the first time in human clinical trials. (*Id.* at 718:20-719:6.) In 2001, CDC-801 was also being evaluated in a phase II clinical trial. (JTX-66.6; Knowles Tr. 1721:1-6.) Phase I and Phase II studies are conducted in humans. (Page Tr. 718:20-21.)

796. A second SelCID that had begun clinical development was CDC-998, which was "approximately 1000-fold more potent than thalidomide in inhibiting TNF-α in LPS stimulated human PBMC." (JTX-66.6; Page Tr. 720:17-721:4; DDX3-29.) Marriott 2001 reports that "CDC-998 has completed initial preclinical safety studies and has now moved forward into a Phase I trial programme that was initiated in the UK at the end of 2000." (JTX-66.6.) CDC-998 was also studied in a dog model and no emetic effects were shown. (*Id.*; Page Tr. 720:17-721:4; Knowles Tr. 1729:18-21; DDX3-29.)

797. As such, Marriott 2001 concludes that "laboratory studies and initial clinical studies are encouraging." (JTX-66.7.) "Bearing in mind the potential clinical efficacy of

thalidomide in a range of conditions with very little therapeutic option it is an exciting prospect that these novel compounds may provide us with a new generation of clinically effective drugs." (*Id.*)

d. Muller 1998

798. George Muller et al., *Thalidomide Analogs and PDE4 Inhibition*, 8 BIOORGANIC & MED. CHEM. LETTERS 2669 (1998) ("Muller 1998"), is an article that was published in 1998, and is authored by one of the inventors of the '536 patent. (JTX-69.1; Page Tr. 713:10-24; DDX3-24.)

799. Muller 1998 discloses that TNF-α "is a key cytokine in the inflammatory cascade" and that "[e]xcessive TNF-α levels have been found to be associated with a number of inflammatory and autoimmune conditions including rheumatoid arthritis." (JTX-69.1.) As such, "control of TNF-α levels could be a key to the treatment of a wide range of diseases." (*Id.*) Muller 1998 teaches that "[t]he validity of this approach has recently been demonstrated by the clinical benefit observed in the treatment of rheumatoid arthritis and Crohn's disease by TNF-α antibodies and TNF-α soluble receptors." (*Id.*)

800. Muller 1998 describes the efforts of Celgene to prepare several analogs of thalidomide and increase their ability to inhibit TNF-α and PDE4 *in vitro* as well as decrease their teratogenic potency. (*Id.*; Page Tr. 713:25-714:20; DDX3-24.)

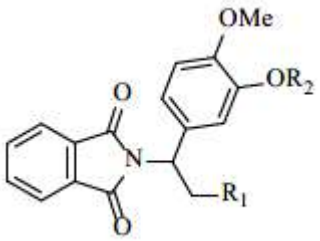
801. Muller 1998 generally discusses thalidomide analogs and their ability to inhibit PDE4 and, therefore, their ability to inhibit TNF-α. (JTX-69.1; Page Tr. 713:25-714:8; DDX3-24.) Muller 1998 states that "[e]xcessive TNF-α levels have been found to be associated with a number of inflammatory and autoimmune conditions including rheumatoid arthritis." (JTX-69.1.) Muller 1998 also teaches that "control of TNF-α levels could be a key to the treatment of a wide range of disease" and that "[t]he validity of this approach has recently been demonstrated

by the clinical benefit observed in the treatment of rheumatoid arthritis and Crohn's disease by TNF-α antibodies and TNF-α soluble receptors." (*Id.*; Page Tr. 713:25-714:8; DDX3-24.)

802. Muller 1998 also discloses that, "[i]n a program to increase the TNF-α inhibitory potency of thalidomide and eliminate/decrease its teratogenic potency we have prepared numerous analogs of thalidomide." (JTX-69.1; Page Tr. 714:9-20; DDX3-24.) Muller 1998 also states that "these thalidomide analogs are potent inhibitors of PDE4" and that "[i]it is proposed that these thalidomide analogs control TNF-α levels by inhibition of PDE4." (JTX-69.5.)

803. Muller 1998 also discloses that "[c]ellular levels of cAMP are controlled by adenylate cyclase and the cAMP phosphodiesterases (PDEs)" and that "PDE4 is the major enzyme found in monocytes, the major producers of TNF-α in the inflammatory cascade." (*Id.* at 2.) Muller 1998 also discloses that "elevated levels of cAMP inhibit TNF-α production in activated monocytes and peripheral blood mononuclear cells (PBMC)." (*Id.* at 1-2; Page Tr. 714:21-715:8; DDX3-25.) Muller 1998 goes on to state that "[i]nhibition of PDE4 has been shown to be an effective method for inhibition of TNF-α production in activated monocytes and PBMC." (JTX-69.2; Page Tr. 714:21-715:8; DDX3-25.)

804. Muller 1998 reports the IC_{50} values for TNF-α and PDE4 inhibition "in LPS stimulated human PBMC" for a select number of compounds, as shown in the table below.



Compd	R_1	R_2	TNFα IC_{50} (μM)	PDE4 IC_{50} (μM)
2a	CO_2Me	Me	2.9	2.5
2b	CO_2Me	Et	0.70	0.23

Compd	R_1	R_2	TNFα IC_{50} (μM)	PDE4 IC_{50} (μM)
2c	CO_2Me	cPentyl	1.6	1.7
3a	$CONH_2$	Me	13	9.4
3b	$CONH_2$	Et	2.7	2.0
3c	$CONH_2$	cPentyl	2.5	1.1
4a	CN	Me	1.7	1.3
4b	CN	Et	0.12	0.13
4c	CN	cPentyl	1.6	0.35

(JTX-69.4, Table 1.)

805. Muller 1998 concludes that, "for the majority of compounds," there is a "good correlation between TNF-α inhibition and PDE4 inhibition" and that the compounds in Table 1 "appear to inhibit TNF-α by elevation of cellular cAMP levels." (*Id.*)

806. Based on the results, Muller 1998 concludes that "these thalidomide analogs are potent inhibitors of PDE4" and "control TNF-α levels by inhibition of PDE4." (*Id.* at 5.)

e. WO '606

807. Defendants' statements above regarding WO '606 are incorporated here. (DFF ¶¶ 503-25.).

f. Takeuchi

808. Defendants' statements above regarding Takeuchi are incorporated here. (*Id.* at ¶¶ 526-31.)

D. The '536 Patent Claims Are Anticipated By The '358 Patent.

1. The '358 Patent Discloses Stereomerically Pure (+)-2-[1-(3-Ethoxy-4-Methoxyphenyl)-2-Methylsulfonylethyl]-4-Acetylaminoisoindoline-1,3-Dione That Comprises Greater Than About 97% by Weight of (+) Isomer.

809. As set forth above, the '358 patent explicitly and inherently anticipates "stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-

acetylaminoisoindoline-1,3-dione" and "a pharmaceutically acceptable salt thereof" as recited in the asserted claims of the '638 patent. (DFF ¶¶ 415-74.).

810. For all the same reasons set forth above, the '358 patent also explicitly and inherently anticipates "stereomerically pure compound comprises greater than about 97% by weight of (+) isomer" as recited in claim 6 of the '536 patent. (*Id.*)

2. Celgene's Admissions Regarding the Disclosure of the '358 Patent.

811. Celgene's statements regarding the disclosure of optical purity support that the '358 patent discloses the "stereomerically pure compound comprises greater than about 97% by weight of (+) isomer" as recited in claim 6 of the '536 patent. (*Id.* at ¶¶ 503-25.)

3. The '358 Patent Discloses the Method of Treatment Limitations in Claim 6 of the '536 Patent.

812. Defendants incorporate by reference the disclosures of the '358 patent discussed above. *Id.* at ¶¶ 749-69. The '358 patent discloses certain compounds, their use in inhibiting phosphodiesterases, particularly PDE4, and in the treatment of diseases mediated by inhibition of PDE4. (DTX-174.3-4 (1:5-11, 4:28-31); Page Tr. 707:12-708:11.) The '358 patent discloses that "[d]ecreasing TNF[-]α levels, increasing cAMP levels, and inhibiting PDE IV thus constitute valuable therapeutic strategies for the treatment of many inflammatory, infectious, immunological or malignant diseases," including psoriasis and rheumatoid arthritis. (DTX-174.4, 13 (4:35-48, 22:29-35 (claims 17-18); Page Tr. 706:10-708:11.) The '358 patent also discloses that "TNF[-]α … plays a role in the area of chronic pulmonary inflammatory diseases," that levels of cAMP "can contribute to inflammatory conditions and diseases," such as asthma, and that "compounds that inhibit PDE IV specifically, would exhibit the desirable inhibition of inflammation and relaxation of airway smooth muscle with a minimum of unwanted side effects, such as cardiovascular or anti-platelet effects." (DTX174.3-4 (2:3-4, 3:66-4:2, 4:23-27).)

813. The '358 patent teaches dosage forms and dose amounts for the compounds of Formula I that are therapeutically effective for treating diseases that are ameliorated by the inhibition of PDE4. In particular, the '358 patent provides that such "compounds can be administered orally, rectally, or parenterally, alone or in combination with other therapeutic agents including antibiotics, steroids, etc., to a mammal in need of treatment." (*Id.* at 6 (7:3-7).)

814. The '358 patent further discloses oral dosage forms, including tablets and capsules "containing from 1 to 100 mg of drug per unit dosage." (*Id.* at 7 (9:22-24); Gilmore Tr. 869:14-18, 870:15-18.) The '358 patent discloses that the compositions can be formulated into:

> physically discrete units suitable as a unitary dosage, or a predetermined fraction of a unitary dose to be administered in a single or multiple dosage regimen to human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with a suitable pharmaceutical excipient.

(DTX-174.7 (9:53-60).) The '358 patent also states that "[p]harmaceutical compositions thus comprise one or more compounds of the present invention associated with at least one pharmaceutically acceptable carrier, diluent or excipient." (*Id.* (9:31-34).) The '358 patent provides that the pharmaceutical compositions "can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders." (*Id.* (9:39-43).) In Examples 22-25, exemplary tablets were prepared containing 100 mg, 75 mg, 10 mg, and 100 mg, respectively, of the active ingredient. (*Id.* at 11-12 (18:7-19:55).)

815. Based on the disclosures in the '358 patent, a POSA would have understood that an oral dosage form containing from 1 to 100 mg of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione would be therapeutically effective for treating psoriasis. (Page Tr. 708:2-20; Gilmore Tr. 869:14-18,

870:15-18.) In addition, the dosage range in the '358 patent (1-100 mg) overlaps considerably with the dosage range in claim 6 of the '536 patent (10-200 mg). (Gilmore Tr. 870:19-23.)

816. The '358 patent also specifically discloses administration in single or multiple doses per day. (DTX-174.7 (9:53-60); Gilmore Tr. 869:25-870:4.)

817. As such, the '358 patent discloses a method of treating psoriasis in a patient through administration of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. (Page Tr. 722:15-723:11; Gilmore Tr. 871:13-23.)

818. Further, a POSA reading the '358 patent would immediately envisage a method of treating psoriasis in a patient through administration of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. (Page Tr. 722:15-723:11; DDX3-32.)

819. Therefore, the '358 patent discloses "[a] method of treating psoriasis, which comprises orally administering to a patient having psoriasis about 10 mg to about 200 mg per day of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, wherein the compound is administered in the form of a tablet or capsule as either a single dose or a divided dose," as recited in the asserted claim of the '536 patent. (Page Tr. 722:15-723:11; Gilmore Tr. 871:13-23.)

820. Therefore, claim 6 of the '536 patent is anticipated by the '358 patent. (Page Tr. 722:15-723:11; Gilmore Tr. 871:13-23.)

E. The '536 Patent Claims Are Obvious.

1. Claim 6 of the '536 Patent Is Obvious Over the '358 Patent and WO '606 in View of Dyke 1999 and Marriott 2001 and the Knowledge of a POSA.

a. Stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione that comprises greater than about 97% by weight of (+) isomer is obvious over the '358 patent and WO '606 and the knowledge of a POSA.

821. As set forth above, "stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione" and "a pharmaceutically acceptable salt thereof," as recited in the asserted claims of the '638 patent, are obvious over the '358 patent in combination with WO '606 and the knowledge of a POSA. (DFF ¶¶ 492-554.)

822. For all the same reasons set forth above, the following claim limitations are obvious over the '358 patent in combination with WO '606 and the knowledge of a POSA: "stereomerically pure compound comprises greater than about 97% by weight of (+) isomer" as recited in claim 6 of the '536 patent. (*Id.*)

b. The method of treatment limitations in claim 6 of the '536 patent are obvious over the '358 patent in view of Dyke 1999 and Marriott 2001 and the knowledge of a POSA.

i. Motivation

823. As of 2002, a POSA would have understood that psoriasis has no cure, and thus the goal of treatment is to decrease the severity and extent of clinical symptoms. (Gilmore Tr. 820:21-24, 824:23-825:12; DTX-215.1; DTX-217.2.) There were a number of conventional topical and systemic therapies that were used and available, but each was associated with its own disadvantages. For example, methotrexate is a systemic drug therapy that has been used for treating psoriasis for the last 50-60 years, and it can work reasonably well in managing the disease. (Gilmore Tr. 878:18-879:1.) The adverse effects, however, can be severe and include

liver damage and osteopathy. (*Id.* at 940:11-14.) As such, patients taking methotrexate need to have their cumulative doses and blood counts monitored on a monthly basis to assess the risk of developing liver and bone disease, respectively. (*Id.* at 940:15-20.)

824. Another commonly used systemic drug therapy was cyclosporine. Patients taking cyclosporine for two weeks or more show rapid improvement. (DTX-217.6.) "However, like other treatments for psoriasis, cyclosporine is not curative, and the disease relapses within days or weeks after the discontinuation of treatment." (*Id.*) Moreover, cyclosporine is associated with the risk of hypertension and kidney disease, and thus it is not suitable for long-term use. (*Id.* at 7; Gilmore Tr. 939:24-940:10).

825. It was known prior to 2002 that increased levels of TNF-α, a pro-inflammatory cytokine, are involved in the pathogenesis of inflammatory skin conditions, such as psoriasis, and thus a POSA would have been motivated to target this pathway in finding an alternative treatment for such diseases. (Page Tr. 705:10-22; DTX-174.3 (1:5-11); DTX-140.1; JTX-67.5; DTX-215.2; DTX-233.1.) Indeed, the '358 patent teaches that "[e]xcessive or unregulated TNF[-]α production … has been implicated in a number of disease conditions," including "endotoxemia and/or toxic shock syndrome; rheumatoid arthritis, Crohn's disease, [inflammatory bowel disease], cachexia and Adult Respiratory Distress Syndrome." (DTX-174.3 (1:21-30) (internal citations omitted); Page Tr. 706:10-21.) The '358 patent discloses that one method of blocking TNF-α production is with monoclonal anti-TNF-α antibodies, which had already been shown to be beneficial in treating in numerous diseases, such as rheumatoid arthritis. (DTX-174.3 (2:35-39).)

826. Another method for inhibiting TNF-α production, as provided in the '358 patent, is by controlling the levels of cAMP. (DTX-174.4 (3:66-4:9, 4:57-63); Page Tr. 706:24-707:11.)

As discussed, cAMP is a secondary messenger that is involved in many biological functions, some of which "can contribute to inflammatory conditions and diseases including asthma, inflammation, and other conditions." (DTX-174.4 (3:66-4:3).) Of relevance, "[i]t has been shown that the elevation of cAMP in inflammatory leukocytes inhibits their activation and the subsequent release of inflammatory mediators, including TNF[-]α." (*Id.* (4:3-6); Page Tr. 706:24-707:11.) The '358 patent provides that "[t]he primary cellular mechanism for the inactivation of cAMP is the breakdown of cAMP by a family of isoenzymes referred to as cyclic nucleotide phosphodiesterases (PDE)." (DTX-174.4 (4:12-14).) "There are seven known members of the family of PDEs," with "the inhibition of PDE type IV [being] particularly effective in both the inhibition of inflammatory mediator release and the relaxation of airway smooth muscle." (*Id.* (4:16-20).)

827. Defendants incorporate by reference the disclosures of the '358 patent, Dyke 1999, and Marriott 2001 discussed above. (DFF ¶¶ 749-97.) Defendants also incorporate by reference the above discussion of the Technical Background. (*Id.* at ¶¶ 708-48.)

828. The '358 patent discloses compounds of Formula I, including apremilast, and their use in inhibiting phosphodiesterases, particularly PDE4, and in the treatment of diseases mediated by inhibition of PDE4. (DTX-174.3-4 (1:5-11, 4:28-31); Page Tr. 707:12-708:11.) The '358 patent discloses that "[d]ecreasing TNF[-]α levels, increasing cAMP levels, and inhibiting PDE IV thus constitute valuable therapeutic strategies for the treatment of many inflammatory, infectious, immunological or malignant diseases," including psoriasis and rheumatoid arthritis. (DTX-174.4, 13 (4:35-48, 22:29-35 (claims 17-18)); Page Tr. 708:2-11.) The '358 patent also discloses that TNF-α "plays a role in the area of chronic pulmonary inflammatory diseases," that levels of cAMP "can contribute to inflammatory conditions and

diseases," such as asthma, and that "compounds that inhibit PDE IV specifically, would exhibit the desirable inhibition of inflammation and relaxation of airway smooth muscle with a minimum of unwanted side effects, such as cardiovascular or anti-platelet effects." (DTX-174.3-4 (2:3-4, 3:66-4:2, 4:23-27); Page Tr. 707:12-24.)

829. Other prior art available as of the 2002 priority date confirms the '358 patent's teachings regarding the use of PDE4 inhibitors to treat inflammation. (JTX-137.1 ("Recent data have shown that PDE4 inhibitors potently suppress TNF[-]α-release from mononuclear phagocytes," which "opened the possibility of using PDE4 inhibitors in the treatment of pathologies associated with over expression and production of TNF[-]α, such as certain auto-immune diseases."); JTX-69.1 ("[C]ontrol of TNF-α levels could be a key to the treatment of a wide range of diseases," and "[t]he validity of this approach has recently been demonstrated by the clinical benefit observed in the treatment of rheumatoid arthritis and Crohn's disease by TNF-α antibodies and TNF-α soluble receptors."); Page Tr. 713:25-714:8; JTX-68.1 ("Recent successful clinical trials in rheumatoid arthritis and inflammatory bowel disease with TNF-α antibodies and soluble TNF-α receptors have validated the inhibition of TNF-α as a clinical treatment."); JTX-67.1 ("The potential use of PDE4 inhibitors as anti-inflammatory agents for the treatment of asthma and other inflammatory disorders has received considerable attention from the pharmaceutical industry."); DTX-159.10 (9:18-28 ("Decreasing TNF[-]α levels, increasing cAMP levels, and inhibiting PDE IV thus constitute valuable therapeutic strategies for the treatment of many inflammatory, infectious, immunological or malignant diseases," including psoriasis and rheumatoid arthritis.); JTX-66.3 ("TNF-α is a key regulator of other pro-inflammatory cytokines and leukocyte adhesion molecules and therefore represents a therapeutic

target in a number of conditions where the overproduction of TNF-α is associated with a pathological inflammatory cascade.").)

830. The '358 patent teaches dosage forms and dose amounts for the compounds of Formula I, including apremilast, that are therapeutically effective for treating diseases that are ameliorated by the inhibition of PDE4. (Page Tr. 708:2-20, 709:11-23; Gilmore Tr. 869:14-18, 870:15-18.) In particular, the '358 patent provides that such compounds "can be administered orally, rectally, or parenterally, alone or in combination with other therapeutic agents including antibiotics, steroids, etc., to a mammal in need of treatment." (DTX-174.6 (7:3-6); Page Tr. 708:12-20, 709:11-24.)

831. The '358 patent further discloses oral dosage forms, including tablets and capsules "containing from 1 to 100 mg of drug per unit dosage." (DTX-174.7 (9:22-24); Gilmore Tr. 869:14-18, 870:15-18.) The '358 patent discloses that the compositions can be formulated into:

> physically discrete units suitable as a unitary dosage, or a predetermined fraction of a unitary dose to be administered in a single or multiple dosage regimen to human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with a suitable pharmaceutical excipient.

(DTX-174.7 (9:53-60).) A POSA would have understood the '358 patent's teaching that the compositions can "be administered in a single or multiple dosage regimen to human subjects and other mammals" to mean once, twice, or three times daily. (Gilmore Tr. 869:25-870:8.) The '358 patent also states that "[p]harmaceutical compositions thus comprise one or more compounds of the present invention associated with at least one pharmaceutically acceptable carrier, diluent or excipient." (DTX-174.7 (9:31-34).) The '358 patent provides that the pharmaceutical compositions "can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, soft and hard gelatin capsules, suppositories, sterile injectable solutions and

sterile packaged powders." (*Id.* (9:39-43).) In Examples 22-25, exemplary tablets were prepared containing 100 mg, 75 mg, 10 mg, and 100 mg, respectively, of the active ingredient. (*Id.* at 11-12 (18:7-19:55).)

832. Dyke 1999 generally discusses the therapeutic potential of PDE4 inhibitors and teaches that "[i]nhibition of PDE4 results in an elevation of cAMP in [inflammatory] cells, which in turn downregulates the inflammatory response. The anti-inflammatory effects of PDE4 inhibitors have been well documented both *in vitro* and *in vivo* in a variety of animal models." (JTX-67.1.) Dyke 1999 specifically looks at the development of PDE4 inhibitors as potential treatments for asthma, allergic rhinitis, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis, multiple sclerosis, inflammatory bowel disease, and other inflammatory diseases. (*Id.* at 2-15.)

833. Dyke 1999 states that PDE4 "is the predominant PDE found in the inflammatory cells associated with asthma." (*Id.* at 5.) Further, the "[i]nhibition of PDE4 results in the elevation of cAMP" and "decrease[s] the release of tumour necrosis factor (TNF)-α from macrophages and monocytes and reduce[s] the production of IL-2, IL-4, IL-5, IL-13 and interferon (IFN)-γ from T-lymphocytes." (*Id.*) Based on known information at the time, "[t]here [was] no doubt that selective PDE4 inhibitors exert potent anti-inflammatory effects *in vitro* and thus should have benefits in the treatment of asthma." (*Id.*) In addition to in vitro testing, "there are several reports describing the *in vivo* activity of a variety of selective PDE4 inhibitors in animal models." (*Id.*)

834. Dyke 1999 further discloses a PDE4 inhibitor that was being dosed at 300 mg "to be effective in reducing TNF levels and lymphocyte proliferation." (*Id.* at 8.) The drug "was

administered to healthy volunteers in a single escalating dose, randomised, placebo-controlled Phase I study." (*Id.*) The drug was dosed up to 400 mg without any adverse events. (*Id.*)

835. Dyke 1999 also shows the results of PDE4 inhibitors in the treatment of rheumatoid arthritis and other conditions associated with joint tissue damage and inflammation and states that there is "considerable evidence now that the pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α are the major contributors to joint tissue damage, inflammation, hyperplasia, pannus formation and bone resorption." (*Id.* at 9.) Furthermore, Dyke 1999 discloses that PDE4 inhibitors were known to "suppress the action of a wide range of inflammatory cells, including basophils, eosinophils, and mast cells" and that PDE4 inhibitors "also possess a very broad *in vitro* anti-inflammatory action *via* inhibition of the release of reactive oxygen species, prostaglandins, and inflammatory cytokines such as IL-5, IFN-γ, and TNF-α." (*Id.* (internal citations omitted).)

836. Because of the pharmacological profile of PDE4 inhibitors, Dyke 1999 concludes that they "also have the potential to address the T-cell component of RA, since they are very effective in inhibiting T-cell proliferation mediated *via* a range of different agents." (*Id.* at 9-10.) Based on these pharmacological properties, it is also stated in the article that "a number of groups … explore[d] the potential of PDE4 inhibitors in animal models of RA." (*Id.* at 10.)

837. This early, preclinical work showed that the use of selective PDE4 inhibitors was able to "reduce disease severity in collagen II induced arthritis" and "streptococcal cell wall-(SCW) induced arthritis" in mice, thereby showing "significant amelioration of disease." (*Id.*) In the clinic, "a small placebo-controlled, double-blind Phase II study" investigated the effect of a selective PDE4 inhibitor, RP73401, in 35 patients with rheumatoid arthritis. (*Id.*) Dyke 1999 reports that RP73401 "was able to induce a positive trend towards clinical improvement," with

"no serious or unexpected adverse events." (*Id.*) Although the "results from this study were not statistically significant," Dyke 1999 provides that "this was probably due to the size of the study and its short duration." (*Id.*)

838. Other than rheumatoid arthritis, other types of arthritis were also investigated for treatment with PDE4 inhibitors. Specifically, the "effect of selective PDE4 inhibitors" was investigated "in both CIA and streptococcal cell wall-(SCW) induced arthritis." (*Id.*)

839. Dyke 1999 also notes the use of PDE4 inhibitors for reducing skin eosinophilia. (*Id.* at 11.) For treatment of atopic dermatitis (AD), topical use of a selective PDE4 inhibitor was evaluated. (*Id.*) "When applied bilaterally over eight days, the compound effectively inhibited all of the inflammation parameters tested and showed both qualitative and quantitative improvements with no adverse effects." (*Id.* (internal citations omitted).) Dyke 1999 therefore concluded that "there may be a role for PDE4 inhibitors in the treatment of AD." (*Id.* at 12.)

840. Based on the use of PDE4 inhibitors to treat rheumatoid arthritis and their "broad spectrum anti-inflammatory action," Dyke 1999 teaches that PDE4 inhibitors "have the potential to provide a beneficial treatment for psoriasis." (*Id.*; Page Tr. 712:8-18.) Accordingly, because Dyke 1999 suggests that PDE4 inhibitors could ameliorate the clinical symptoms of rheumatoid arthritis and other inflammatory conditions, it would have been reasonable for a POSA to expect that PDE4 inhibitors could be therapeutically useful for psoriasis as well. (Page Tr. 712:8-18.)

841. Dyke discloses that, "[w]ith regard to the inflammatory component of the disease, PDE4 inhibitors have been shown to inhibit the inflammatory response of a number of mediators *via* either topical or systemic administration." (JTX-67.12. (internal citations omitted).)

842. Dyke 1999 states:

> The exact cause of psoriasis is unknown, although it appears to be an autoimmune disease with a likelihood for genetic predisposition. There is a large T-cell

> infiltration in the affected regions of the skin, with CD4+ lymphocytes in the dermis and CD8+ lymphocytes in the epidermis. These lymphocytes secrete IL-2, IFN-γ, and TNF-α which alter keratinocyte proliferation and differentiation. In addition, 5-10% of psoriasis patients develop psoriatic arthritis, with symptoms that are very similar to [rheumatoid arthritis]."

(*Id.* (internal citations omitted).)

843. Dyke 1999 discloses that "a number of groups have investigated the effect of PDE4 inhibitors on skin." (*Id.*) These studies showed that the PDE4 inhibitor Ro20-1724 led to a three-fold increase in cAMP concentrations in epidermal cells, thereby "suggesting that PDE4 inhibitors may be potentially beneficial in psoriasis." (*Id.*) PDE4 inhibitors were also shown to "inhibit the inflammatory response of a number of mediators *via* either topical or systemic administration." (*Id.* (internal citations omitted).) In addition, Dyke 1999 provides that Ro20-1724 was investigated clinically in "two double-blind studies comparing its effectiveness to vehicle." (*Id.*; Page Tr. 712:20-713:4.) The results from the clinical study showed that PDE4 inhibition "improve[d] psoriatic lesions" and "had no adverse systemic or cutaneous effects, [again,] suggesting the therapeutic potential of such compounds in the treatment of psoriasis." (JTX-67.12; Page Tr. 712:20-713:4.)

844. In light of the teachings of the '358 patent and Dyke 1999 regarding the therapeutic potential of PDE4 inhibition for treating inflammatory diseases like psoriasis, a POSA would have further looked to Marriott 2001, which confirms that thalidomide analogs were known to be potent PDE4 inhibitors. (Page Tr. 717:12-21.)

845. Marriott 2001 generally discusses thalidomide analogues and discloses that thalidomide was "established as an effective immunomodulatory and anti-inflammatory drug" that showed potential in treating a range of conditions, including rheumatoid arthritis. (JTX-66.2-3; Page Tr. 716:15-20.) Marriott 2001 further states that "[t]halidomide is a clinically effective compound that has shown activity in a wide variety of inflammatory and autoimmune

diseases and in cancer." (JTX-66.4.) Marriott 2001 confirms that thalidomide has been shown to inhibit TNF-α, which is "a key regulator of other pro-inflammatory cytokines and leukocyte adhesion molecules and therefore represents a therapeutic target in a number of conditions where the overproduction of TNF-α is associated with a pathological inflammatory cascade." (*Id.* at 3.) "In particular, thalidomide has shown potential for the treatment of a range of conditions, including rheumatoid arthritis (RA), the inflammatory and wasting effects of chronic tuberculosis, Behcet's disease and Crohn's disease." (*Id.* (internal citations omitted).) Its "[c]linical activity *in vivo* is attributed to the wide ranging immunological and non-immunological properties possessed by this drug; these includes anti-TNF-α, T-cell co-stimulatory, anti-angiogenic activities and also direct antitumour activity." (*Id.* at 2.) Indeed, the FDA approval of Enbrel, a TNF-α receptor for the treatment of rheumatoid arthritis, and Infliximab, a TNF-α antibody for treating Crohn's disease, have "validated TNF-α blockage as therapeutic treatment." (*Id.* at 3.)

846. Marriott 2001 also discloses that in 1960, there were reports associating thalidomide with neuropathies and birth defects, and that "it would seem likely that novel compounds designed using thalidomide structure as a lead would allow optimisation of its immunological and anticancer properties while decreasing its side effects." (*Id.* at 2, 4; Page Tr. 716:4-9.) This investigation led to the synthesis of two categories of analogs, with "greatly enhanced immunological activity and with similarly decreased toxicity"—selective cytokine inhibitory drugs (SelCIDs), which are PDE4 inhibitors, and immunomodulatory drugs (IMiDs), which do not inhibit PDE4 but act via an unknown mechanism. (JTX-66.2, 4.)

847. Marriott 2001 notes that "Celgene Corporation initiated a medicinal chemistry program to design and prepare thalidomide analogues," with a focus being to improve its anti-

TNF-α properties. (*Id.* at 4; Page Tr. 716:4-9.) Marriott 2001 discloses that one subset of thalidomide analogs is termed selective cytokine inhibitory drugs (SelCIDs), which are PDE4 inhibitors. (Page Tr. 717:12-21.) Marriott 2001 further states that the SelCID analogues disclosed in Table 1 "are potent PDE4 inhibitors." (JTX-66.4-5 (Table 1); Page Tr. 717:12-21.) Marriott 2001 confirms that Celgene Corporation's PDE4 inhibitor agents CDC-801 and CDC-998, both thalidomide analogs and selective cytokine inhibitory drugs (SelCIDs), were known to be under clinical development in November of 1999, well before the filing date of the patents-in-suit. (JTX-66.6; Page Tr. 717:22-718:13, 720:17-721:4.) Marriott 2001 generally describes aspects of two clinical trials in particular that were related to CDC-801. (*See* JTX-66.6 ("Clinical development of SelCID analogues"); Page Tr. 718:8-13.)

848. A Phase I trial in the UK showed that the thalidomide analog CDC-801, a 10-fold more potent TNF-α inhibitor than thalidomide, had no serious adverse effects. (JTX-66.6; Page Tr. 718:8-18.) Another thalidomide analog, CDC-998, which was "approximately 1000-fold more potent than thalidomide in inhibiting TNF-α in LPS stimulated human PBMC," had completed initial preclinical safety studies and moved forward to a Phase I trial initiated at the end of 2000. (JTX-66.6; Page Tr. 720:17-721:4.)

849. Accordingly, Marriott 2001 reports that "laboratory studies and initial clinical studies are encouraging." (JTX-66.7.) Marriott 2001 ultimately concludes that "[b]earing in mind the potential clinical efficacy of thalidomide in a range of conditions with very little therapeutic option it is an exciting prospect that these novel compounds may provide us with a new generation of clinically effective drugs." (*Id.*)

850. Other prior art available as of the 2002 priority date confirms the teachings of Marriott 2001. (*See* JTX-69.5 (disclosing thalidomide analogs that are "potent inhibitors of

PDE4" and are able to "control TNF-α levels by inhibition of PDE4"); Page Tr. 713:25-714:8; JTX-68.2 (teaching that "thalidomide analogs … are … potent inhibitors of phosphodiesterase type 4 (PDE4)" and the "PDE4 inhibitory potency for most of these compounds has correlated with their TNF-α inhibitory activity").)

851. Marriott 2001 further confirms the teachings of the '358 patent that thalidomide analogs, such as (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, can potently inhibit PDE4 and are therapeutically useful for treating a wide range of inflammatory diseases, such as psoriasis. (Page Tr. 717:12-21.) In light of the teachings of the '358 patent, in view of Dyke 1999 and Marriott 2001, a POSA would have been motivated to further develop thalidomide analogs with PDE4 inhibitory activity to treat psoriasis, with a reasonable expectation of success. (*Id.* at 723:14-19, 724:20-725:11.)

852. A POSA would have been motivated to combine the '358 patent with Dyke 1999 and Marriott 2001, as each of these references discuss PDE4 inhibiting compounds for the treatment of inflammatory conditions, including psoriasis. (*Id.*; DDX3-33.)

ii. Reasonable expectation of success

853. The '358 patent disclosed and/or taught steromerically pure (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, its use in the inhibition of PDE4, and the treatment of diseases mediated by PDE4 inhibition, including psoriasis. (*Id.* at 722:15-723:11.) A POSA reviewing Dyke 1999 would have known that PDE4 inhibitors had been demonstrated to have anti-inflammatory effects, given that inhibition of PDE4 results in the elevation of cAMP, which thereby decreases the release of TNF-α from macrophages and monocytes. (*Id.* at 711:9-16.) Dyke 1999 also taught the use of PDE4 inhibitors in the treatment of rheumatoid arthritis and that these compounds had the potential to treat psoriasis. (*Id.* at 712:8-15.)

854. A POSA would have known that PDE4 had been implicated in the pathogenesis of inflammatory diseases and that PDE4 was present in the majority of inflammatory cells. (*Id.* at 701:5-9; DDX3-10.) A POSA would have also been well aware that selective PDE4 inhibitors had broad anti-inflammatory activity (Page Tr. 702:13-21; DDX3-10) and could suppress the release of a range of inflammatory mediators from inflammatory cells (Page Tr. 702:22-703:8; DDX3-10). Therefore, a POSA would have been motivated to develop selective PDE4 inhibitors to treat a wide range of inflammatory diseases. (Page Tr. 700:22-701:4; DDX3-9.)

855. A POSA also would have known that psoriasis is an inflammatory disease (Page Tr. 705:10-12; DTX-140.1) and is characterized by hyperproliferation of keratinocytes (DTX-140.1). Further, a POSA would have known that psoriasis is associated with an excessive release of inflammatory mediators, particularly TNF-α. (Page Tr. 705:10-19.) A POSA would also have known that levels of TNF-α produced by PBMC obtained from psoriasis patients showed that TNF-α produced by these cells is significantly higher compared to the levels produced by PBMC obtained from healthy subjects. (*Id.* at 705:10-22; DTX-140.1; DDX3-14.) Therefore, a POSA would have been motivated to reduce levels of TNF-α in a person with psoriasis, to contribute to an anti-inflammatory effect. (*Id.*; DTX-140.1; DDX3-14.)

856. A POSA reading Marriott 2001 would have known that thalidomide was an established anti-inflammatory drug with potential use in treating various conditions including rheumatoid arthritis (JTX-66.2-3) and that a subset of thalidomide analogues called SelCIDs were PDE4 inhibitors and could have been used to inhibit TNF-α (*id.* at 4; Page Tr. 717:12-21; DDX3-28). As a POSA would have known that PDE4 inhibitors could treat rheumatoid arthritis through inhibition of TNF-α (JTX-66.3), as well as potentially treat the inflammatory condition psoriasis, a POSA would have been motivated to use (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-

methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione (a PDE4 inhibitors disclosed in the '358 patent) to treat such psoriasis. (Page Tr. 712:8-18, 723:14-19, 724:20-725:11; JTX-67.12; DDX-3-22.)

857. Based on the foregoing, a POSA reading the '358 patent, in view of Marriott 2001 and Dyke 1999, and in view of the POSA's knowledge, would have been motivated, with a reasonable expectation of success, to treat psoriasis in a patient through administration of stereomerically pure (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. (Page Tr. 697:4-8, 723:14-19, 724:20-725:11; DDX3-32.)

858. Therefore, "a method of treating psoriasis, which comprises orally administering to a patient having psoriasis about 10 mg to about 200 mg per day of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, wherein the compound is administered in the form of a tablet or capsule as either a single dose or a divided dose," as recited in asserted claim 6 of the '536 patent, is obvious over of the '358 patent and WO '606 in view of Dyke 1999 and Marriott 2001, and the knowledge of a POSA, and a POSA would have been motivated with a reasonable expectation of success to practice the method of claim 6. (Gribble Tr. 601:14-19; Page Tr. 697:4-8, 723:14-19, 724:20-725:11; Gilmore Tr. 874:21-875:8.)

2. Claim 6 of the '536 Patent Is Obvious Over the '358 Patent and Takeuchi In View of Dyke 1999 and Marriott 2001 and the Knowledge of a POSA

a. The stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione that comprises greater than about 97% by weight of (+) isomer is obvious over the '358 patent and Takeuchi and the knowledge of a POSA.

859. As set forth above, "stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione," and "a pharmaceutically acceptable

salt thereof," as recited in the asserted claims of the '638 patent, are obvious over the '358 patent in combination with Takeuchi and the knowledge of a POSA. (DFF ¶¶ 492-554.)

860. For all the same reasons set forth above, the following claim limitations are obvious over the '358 patent in combination with Takeuchi and the knowledge of a POSA: "stereomerically pure compound comprises greater than about 97% by weight of (+) isomer," as recited in claim 6 of the '536 patent. (*Id.*)

b. The method of treatment limitations in claim 6 of the '536 patent are obvious over the '358 patent in view of Dyke 1999 and Marriott 2001, and the knowledge of a POSA.

861. For the same reasons discussed above (*id.* at ¶¶ 821-58), a POSA reading the '358 patent, in view of Marriott 2001 and Dyke 1999, and in view of the POSA's knowledge, would have been motivated, with a reasonable expectation of success, to treat psoriasis in a patient through administration of stereomerically pure (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. (Page Tr. 697:4-8, 723:14-19, 724:20-725:11; DDX3-32.)

862. Therefore, "a method of treating psoriasis, which comprises orally administering to a patient having psoriasis about 10 mg to about 200 mg per day of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, wherein the compound is administered in the form of a tablet or capsule as either a single dose or a divided dose," as recited in asserted claim 6 of the '536 patent, is obvious over of the '358 patent and Takeuchi in view of Dyke 1999 and Marriott 2001, and the knowledge of a POSA, and a POSA would have been motivated with a reasonable expectation of success to practice the method of claim 6. (Gribble Tr. 609:1-7; Page Tr. 697:4-8, 723:14-19, 724:20-725:11; Gilmore Tr. 874:21-875:8.)

3. Claim 6 of the '536 Patent Is Obvious Over the '358 Patent in View of Dyke 1999, Marriott 2001, and Muller 1998, and the Knowledge of a POSA.

a. The stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione that comprises greater than about 97% by weight of (+) isomer is obvious over the '358 patent and the knowledge of a POSA.

863. As set forth above, "stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione," and "a pharmaceutically acceptable salt thereof," as recited in the asserted claims of the '638 patent, are disclosed in the '358 patent. (DFF ¶¶ 415-74.)

864. For all the same reasons set forth above, the following claim limitations are disclosed in the '358 patent: "stereomerically pure compound comprises greater than about 97% by weight of (+) isomer," as recited in claim 6 of the '536 patent. (*Id.*)

b. The method of treatment limitations in claim 6 of the '536 patent are obvious over the '358 patent in view of Dyke 1999, Marriott 2001, and Muller 1998, and the knowledge of a POSA.

i. Motivation

865. For the same reasons discussed above (*id.* at ¶¶ 821-62), a POSA would have been motivated to further develop thalidomide analogs with PDE4 inhibitory activity to treat psoriasis, with a reasonable expectation of success, in light of the teachings of the '358 patent, in view of Dyke 1999 and Marriott 2001. (Page Tr. 697:4-8, 723:14-19, 724:20-725:11.)

866. Defendants incorporate by reference the disclosures of Muller 1998 discussed above. (DFF ¶¶ 798-806.)

867. A POSA would have been motivated to combine the '358 patent with Dyke 1999, Marriott 2001, and Muller 1998, as each of these references discuss PDE4 inhibiting compounds. (Page Tr. 723:14-25, 724:20-725:11.)

ii. Reasonable expectation of success

868. A POSA reading Marriott 2001 would have known that thalidomide was an established anti-inflammatory drug with potential use in treating various conditions including rheumatoid arthritis (JTX-66.2-3) and that a subset of thalidomide analogues called SelCIDs were PDE4 inhibitors and could have been used to inhibit TNF-α (*id.* at 4; Page Tr. 717:12-21; DDX3-28). Muller 1998 would have further confirmed that thalidomide analogues inhibit PDE4 and therefore inhibit production of TNF-α and disclosed that excessive TNF-α levels were associated with inflammatory conditions such as rheumatoid arthritis. (Page Tr. 713:25-714:8.) As a POSA would have known that PDE4 inhibitors could treat rheumatoid arthritis through inhibition of TNF-α, as well as potentially treat the inflammatory conditions psoriasis, a POSA would have been motivated to use (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione (a PDE4 inhibitor disclosed in the '358 patent) to treat psoriasis. (*Id.* at 712:8-18; JTX-67.12; DDX-3-22.)

869. Based on the foregoing, a POSA reading the '358 patent, in view of Marriott 2001, Dyke 1999, and Muller 1998, and in view of the POSA's knowledge, would have been motivated, with a reasonable expectation of success, to treat inflammatory diseases, including diseases or disorders ameliorated by the inhibition of PDE4 (such as psoriasis and the arthritic condition psoriatic arthritis), in a patient through administration of stereomerically pure (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. (Page Tr. 697:4-8, 723:14-19, 724:20-725:11; DDX3-32.)

870. Therefore, "a method of treating psoriasis, which comprises orally administering to a patient having psoriasis about 10 mg to about 200 mg per day of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione,

wherein the compound is administered in the form of a tablet or capsule as either a single dose or a divided dose," as recited in the asserted claim of the '536 patent is obvious over of the '358 patent in view of Dyke 1999, Marriott 2001, and Muller 1998, and the knowledge of a POSA, and a POSA would have been motivated with a reasonable expectation of success to practice the method of claim 6. (Gribble Tr. 590:14-19; Page Tr. 697:4-8, 723:14-19, 724:20-725:11; Gilmore Tr. 874:21-875:8).

871. Amgen's expert, Dr. Knowles, testified that a POSA would not have been able to use apremilast to treat psoriasis, as required by asserted claim 6 of the '536 patent, with a reasonable expectation of success given the lack of data in the prior art. Knowles Tr. 1661:6-12. In particular, Dr. Knowles testified that a POSA would not have any knowledge regarding the safety or tolerability of apremilast in treating psoriasis, or whether apremilast has any desirable properties. Knowles Tr. 1692:11-12, 1692:17-19. Thus, Dr. Knowles claims that without any information regarding the "therapeutic index" of apremilast, "whether it was safe, whether it was potent, and whether it had drug-like properties," a POSA would not have any reason to expect apremilast to be successful to treat psoriasis. Knowles Tr. 1693:7-12. Dr. Knowles further stated that there was "not enough data" in the prior art "to really be sure whether [thalidomide analogs] would work or not." Knowles Tr. 1700:11-16.

872. However, the '536 patent itself does not disclose which doses of apremilast are safe and effective for administration to patients with psoriasis. Gilmore Tr. 834:6-9. Nor is there any clinical data presented in the '536 patent relating to the safety and efficacy of apremilast, at any doses, for treating psoriasis in a human patient. Gilmore Tr. 834:10-12, 946:18-20; Alexis Tr. 1802:20-23 (testifying that he does not recall seeing any clinical data in

the ’536 patent regarding the administration of apremilast to humans), 1816:18-25 (agreeing that he “did not point to any human data related to this broad range of doses” in the ’536 patent).

VI. Objective Indicia Of Nonobviousness Support A Finding Of Obviousness for the ’638 and ’536 Patents.

1000. There is no evidence of secondary considerations of non-obviousness that overcome the *prima facie* case of obviousness discussed above.

A. The Therapeutic Index Of Apremilast Does Not Support Nonobviousness.

1001. Dr. Knowles referred to the concept of a drug’s therapeutic index during his testimony on certain asserted secondary considerations for the ’638 and ’536 patents. *See, e.g.*, Knowles Tr. 207:4-11.

1002. A therapeutic index is a measurement of a drug’s comparative efficacy and toxicity or tolerability. Knowles Tr. 207:14-17.

1003. A higher therapeutic index for a drug is preferable to a lower therapeutic index. Knowles Tr. 207:14-208:3.

1004. The therapeutic index of a compound is not an absolute number. Page Tr. 726:8-19.

1005. The same drug can have different values for the therapeutic index, depending on various factors, including the adverse effect being measured. Page Tr. 726:15-727:1.

1006. One therapeutic index value does not measure all toxicity associated with a drug. Knowles Tr. 250:4-6.

1007. The therapeutic index for one compound can also vary depending on what species is used in the relevant experiments. *See* Page Tr. 726:15-727:1.

1008. A high therapeutic index in animal models does not guarantee that a compound will be safe and effective in humans. Knowles Tr. 207:14-25.

1009. The therapeutic window is a concept related to the therapeutic index and is a measure of a dosing range of a drug for which there is efficacy, as well as no problems with tolerability. Knowles Tr. 208:10-17.

1. Amgen's therapeutic index of 12 for apremilast was calculated in Celgene's confidential study and uses only emetic episodes as the relevant side effect.

1010. Amgen's experts discussed a value of 12 for the therapeutic index of apremilast by relying on a confidential Celgene Study Report titled "Therapeutic Index of SelCIDs in Ferret Lung Neutrophilia and Emesis Model." Schafer Tr. 158:2-11; Knowles Tr. 235:7-16; Knowles Tr. 236:14-19; Page Tr. 727:6-13; JTX-118.1, 15; PTX 374.1, 15.

1011. In the ferret model discussed in Celgene's Study Report ("Celgene's Ferret Study"), apremilast's therapeutic index of 12 takes into account only one side effect (i.e., emetic episodes), and it does not account for other side effects. Page Tr. 726:9-727:1.

1012. Apremilast's therapeutic index of 12 for apremilast was obtained by dividing the threshold emetic dose by the ED_{50} value for inhibition of LPS-induced neutrophilia. Schafer Tr. 158:2-11; Page Tr. 729:15-25; JTX-118.15; PTX-374.15.

1013. The threshold emetic dose is the dose at which the ferrets first demonstrated retching or emesis. Page Tr. 729:5-10.

1014. Emesis is another word for vomiting. Page Tr. 729:13-14; Schafer Tr. 151:4-5.

1015. In Celgene's Ferret Study, neutrophils enter the lungs of the ferrets in response to exposure to the agent called LPS or lipopolysaccharide. Page Tr. 728:18-20.

1016. The ED_{50} value for inhibition of LPS-induced neutrophilia is a measurement of the inflammatory response in the ferrets and is the effective dose of the drug that results in 50% inhibition of the infiltration of neutrophils. Page Tr. 728:14-25.

1017. CC-10004 and CC-110004 were Celgene's internal names for the compound apremilast. Schafer Tr. 145:2-3; Knowles Tr. 236:10-13.

1018. Apremilast (CC-10004) had a threshold emetic dose of 10 mg/kg. Page Tr. 729:5-12; JTX-118.15; PTX-374.15.

1019. The threshold emetic dose for apremilast was determined based on the fact that, at a dose of 10 mg/kg of apremilast (CC-10004), two out of the six ferrets in Celgene's study exhibited retching. Page Tr. 733:16-734:7; JTX-118.9 (Table 1); PTX-374.9 (Table 1).

1020. Apremilast (CC-10004) had an ED_{50} value for inhibition of LPS-induced neutrophilia of 0.8 mg/kg. Page Tr. 728:14-729:3; PTX-374.15 (Table 4); JTX-118.15 (Table 4).

1021. Apremilast's therapeutic index of 12 was obtained by dividing the threshold emetic dose of 10 mg/kg by the ED_{50} value for inhibition of LPS-induced neutrophilia of 0.8 mg/kg. Schafer Tr. 158:2-11; Page Tr. 729:15-25; JTX-118.15; PTX-374.15.

1022. The actual value of apremilast's therapeutic index in Celgene's Ferret Study using the reported values of the threshold emetic dose and ED_{50} value for inhibition of LPS-induced neutrophilia for should be 12.5, based on dividing 10 mg/kg by 0.8 mg/kg. Page Tr. 729:15-23. However, 12 is the therapeutic index for apremilast that is reported in Celgene's Study Report. *Id.*; JTX-118.15; PTX-374.15.

1023. Apremilast's therapeutic index of 12 is not related specifically to the treatment of psoriasis. Knowles Tr. 252:21-254:3.

1024. The therapeutic index in Celgene's Ferret Study does not provide useful information in designing a drug formulation for a particular disease; rather, it only gives an early indication of potential toxicity. Page Tr. 736:17-21.

1025. A regulatory agency would be more interested in 28-day dosing of a drug in two species (that is, chronic studies – as opposed to acute studies) to inform a dose that would be used in humans for the first time. Page Tr. 735:23-736:14; *see also* Knowles Tr. 209:7-22.

1026. The FDA would not rely solely on data from an acute study in ferrets to define the therapeutic index (or therapeutic window) for a drug. Page Tr. 736:17-23.

2. Celgene measured other behavioral changes in its Ferret Model that could have been used to calculate the therapeutic index for apremilast, resulting in a lower value.

1027. As of 1999, nausea was known to be another side effect associated with PDE4 inhibitors. Knowles Tr. 250:21-251:1.

1028. Nausea may be worse than vomiting, and a person may vomit in order to rid themselves of nausea. Page Tr. 730:21-731:8.

1029. Humans typically exhibit the unpleasant behavioral effects of nausea before they vomit. Page Tr. 792:17-293:5.

1030. Therefore, relying on emetic episodes as an endpoint in measuring the therapeutic window, as compared to nausea, leads to an overestimate of the therapeutic window. *Id*.

1031. Apremilast's therapeutic index of 12 in Celgene's Ferret Study did not take nausea into account. Knowles Tr. 251:2-6; *see* PDX4-10.

1032. In Celgene's Ferret Study, Celgene measured additional parameters other than emetic effects (retching and vomiting), such as the following behavioral changes: salivation, panting, mouth clawing, flattened posture, ataxia, lip licking, and backward walking. Page Tr. 730:1-20; JTX-118.9; PTX-374.9.

1033. These behavioral changes were measured in order to provide an idea of how well the ferret was tolerating the administered drug and to determine whether the ferret was

potentially experiencing any distress, including whether the ferrets were experiencing nausea. Schafer Tr. 182:8-16; Page Tr. 731:3-18; Page Tr. 732:8-24.

1034. Celgene itself noted that these behavioral changes were important, describing them as "key parameters" in the study. Page Tr. 732:24-733:15; JTX-118.1; PTX-374.1.

1035. If Celgene had used these other behavioral changes to calculate the relevant threshold emetic dose for apremilast, the therapeutic index for apremilast in Celgene's Ferret Study would change. Page Tr. 734:8-735:7.

1036. As one example, when apremilast was administered at 1.0 mg/kg, the ferrets demonstrated both flattened posture and lip licking. Page Tr. 734:8-22; JTX-118.9 (Table 4); PTX-374.9 (Table 4). Therefore, if these side effects were used to measure the therapeutic index, the relevant threshold dose could be considered to be 1.0 mg/kg. Page Tr. 734:8-22; JTX-118.9 (Table 4); PTX-374.9 (Table 4).

1037. Then to obtain the therapeutic index for apremilast, one would divide the threshold dose of 1.0 mg/kg by the ED_{50} value for inhibition of LPS-induced neutrophilia of 0.8 mg/kg, resulting in a therapeutic index of 1.25. Page Tr. 734:8-22; JTX-118.9 (Table 4); PTX-374.9 (Table 4). This lower therapeutic index of 1.25 would be worse than a therapeutic index of 12, as a higher therapeutic index for a drug is preferable to a lower therapeutic index. Knowles Tr. 207:14-208:3.

1038. As a second example, when apremilast was administered at 0.1 mg/kg, the ferrets also demonstrated lip licking. Page Tr. 734:23-735:3; JTX-118.9 (Table 4); PTX-374.9 (Table 4). Therefore, if lip licking were used to measure the therapeutic index, the relevant threshold dose could be considered to be 0.1 mg/kg. Page Tr. 734:23-735:3; JTX-118.9 (Table 4); PTX-374.9 (Table 4).

1039. Then to obtain the therapeutic index for apremilast, one would divide the threshold dose of 0.1 mg/kg by the ED_{50} value for inhibition of LPS-induced neutrophilia of 0.8 mg/kg, resulting in a therapeutic index of approximately 0.1. Page Tr. 734:23-735:3; JTX-118.9 (Table 4); PTX-374.9 (Table 4). This lower therapeutic index of 0.1 would be worse than a therapeutic index of 12. Knowles Tr. 207:14-208:3.

1040. This demonstrates that there is no single therapeutic index value for one drug, as the value of the therapeutic index depends on what side effect is used as the relevant endpoint. Page Tr. 735:4-7.

3. The therapeutic index of 12 is based only on the side effect of emetic episodes and does not take into account other relevant side effects.

1041. Other adverse effects relevant to the use of a PDE4 inhibitor could have been used to calculate a therapeutic index value for PDE4 inhibitors. Page Tr. 726:15-727:1.

1042. As of 1999, PDE4 inhibitors were known to be associated with side effects other than nausea and emesis, such as cardiovascular side effects including vasculitis. Page Tr. 735:8-22; Knowles Tr. 249:23-25; Knowles Tr. 251:15-20.

1043. Vasculitis is inflammation of the blood vessels, which causes changes in the blood vessel walls, including thickening, weakening, narrowing, or scarring. Knowles Tr. 251:21-24.

1044. Vasculitis was an issue raised by FDA in connection with its analysis of cilomilast Knowles Tr. 252:2-4.

1045. Vasculitis would be more likely to be seen in a chronic study (i.e., when a drug is administered over multiple days). Page Tr. 735:8-19.

1046. Psoriasis is a chronic condition. Page Tr. 736:15-16.

1047. However, Celgene's Ferret Study was an acute model. Page Tr. 735:23-736:1.

1048. Therefore, for the foregoing reasons, a therapeutic index of 12 for apremilast in Celgene's Ferret Study using only emetic episodes as the relevant side effect is not persuasive evidence of Amgen's (and Dr. Knowles's) asserted secondary considerations.

B. Dr. Knowles Did Not Present Evidence of a Long-felt, Unmet Need that Supports the Non-Obviousness of the Asserted Claims of the '638 and the '536 Patents.

1. Dr. Knowles's alleged long-felt, unmet need was not clearly defined.

1049. Dr. Knowles stated that there was a "long-felt need for a PDE4 inhibitor suitable for use as a pharmaceutical composition, one that was effective and minimized side effects." Knowles Tr. 217:20-218:1; PDX4-14. He also said that there was "a long-felt need for a PDE4 inhibitor of the appropriate properties." Knowles Tr. 218:21-22. Dr. Knowles opined that apremilast met the long-felt need for a PDE4 inhibitor suitable for use as a pharmaceutical composition, one that was effective and minimized side effects. Knowles Tr. 217:20-218:1; PDX4-14.

1050. Dr. Knowles did not opine that there was a long-felt need for a PDE4 inhibitor to treat a particular disease. Knowles Tr. 254:21:255:6; PDX4-14.

1051. Along the same lines, Dr. Knowles testified that apremilast delivered "a selective PDE4 inhibitor with suitable potency, safety, drug-like properties, and a sufficiently high therapeutic index to make it suitable for a pharmaceutical composition to treat humans." Knowles Tr. 219:8-12. Thereby, Dr. Knowles implied that apremilast could meet his alleged need before it obtained FDA approval. (*Id.*).

1052. However, he also testified more particularly that "there is a medicine in apremilast that has – it fills a substantial need in patients who have psoriasis, psoriatic arthritis, and Behçet disease" (Knowles Tr. 220:10-15), even though those diseases or conditions were not

mentioned in his alleged need. Knowles Tr. 217:20-218:1; PDX4-14. Therefore, Dr. Knowles also implied that the need was met when apremilast obtained FDA approval.

1053. Dr. Knowles did not opine that there was a long-felt need for a pharmaceutical composition comprising stereomerically pure apremilast suitable for oral administration to a patient. Knowles Tr. 242:5-243:22.

1054. It was also unclear whether Dr. Knowles was relying on apremilast's therapeutic index of 12 in Celgene's Ferret Study to support his alleged long-felt need. *See* Knowles Tr. 219:9-13 (testifying that apremilast delivered "a selective PDE4 inhibitor with suitable potency, safety, drug-like properties, and a *sufficiently high therapeutic index* to make it suitable for a pharmaceutical composition to treat humans") (emphasis added).) However, any such reliance is improper due to the problems discussed with this measurement above. DFF ¶¶ 1001-1048. Therefore, a therapeutic index of 12 for apremilast in Celgene's Ferret Study does not demonstrate that apremilast met any alleged long-felt need.

2. The PDE4 inhibitor roflumilast would have met Dr. Knowles's alleged need, as it had suitable properties and was FDA-approved.

1055. The oral PDE4 inhibitor roflumilast obtained FDA approval in 2011, prior to apremilast obtaining FDA approval. Page Tr. 787:9-15.

1056. Roflumilast is a PDE4 inhibitor suitable for use as a pharmaceutical composition. Page 787:16-18; Knowles Tr. 254:12-18.

1057. Roflumilast was effective and minimized side effects, and was approved by the FDA. Knowles Tr. 254:19-22.

1058. The oral PDE4 inhibitor roflumilast obtained FDA approval in 2011, prior to Otezla® (apremilast) obtaining FDA approval. Page Tr. 787:9-15; Schafer Tr. 169:3-9; Schafer Tr. 168:11-14.

1059. Otezla® (apremilast) did not obtain FDA approval until 2014. Schafer Tr. 169:3-9; Schafer Tr. 168:11-14.

3. Dr. Knowles improperly failed to consider whether other compounds, including Example 12, that entered clinical studies in humans may have met his alleged long-felt need.

1060. To the extent Amgen contends that apremilast met Dr. Knowles's alleged need due to the compound apremilast having "suitable potency, safety, drug-like properties, and a sufficiently high therapeutic index to make it suitable for a pharmaceutical composition to treat humans" (Knowles Tr. 219:8-12), as of the priority date, there were PDE4 inhibitors that had demonstrated suitable drug-like properties.

1061. As of at least 2001 (JTX-66.6), Example 12 of the '358 patent (CDC-998) had been advanced into clinical studies in humans. Schafer Tr. 162:20-163:1; *see also* PDX3-2; JTX-208.70.

1062. As of 1999, the PDE4 inhibitor cilomilast was in phase 3 clinical trials in humans. PDX4-12; JTX-67.5.

1063. In fact, Dr. Knowles also discussed five compounds that were in phase 1 clinical studies (CI-1018, T-440, YM-58997, D-22888, and arofylline), and three compounds that were in phase 2 clinical studies (CDC-801, V-11294A, and atizoram), as of October 1999. (*See* Knowles Tr. at 213:23-214:2; PDX4-12.) Therefore, Dr. Knowles's analysis of whether his alleged long-felt unmet need was improper, as he failed to consider whether any of the compounds in human clinical trials as of 1999 could have met his alleged need.

1064. For the foregoing reasons, Amgen and Dr. Knowles have not put forth persuasive evidence of a long-felt unmet need..

C. There is No Evidence of Failures of Others that Supports the Non-Obviousness of the Asserted Claims of the '638 and the '536 Patents.

1065. Dr. Knowles testified that apremilast "succeeded where many other PDE4 inhibitors had failed." Knowles Tr. 198:24-199:8; PDX4-3.

1066. However, Dr. Knowles never provided a clear definition of what would and would not constitute a failure. *See generally* Knowles Tr. 220:16-232:9.

1067. To the extent Amgen relies on apremilast's therapeutic index of 12 in Celgene's Ferret Study to support its argument of failures of others, this is not persuasive due to the problems discussed with this measurement above. DFF ¶¶ 1001-1048.

1068. One of Dr. Knowles's potential definitions of failure could be if a PDE4 inhibitor did not receive FDA approval. Knowles Tr. 243:23-244:8.

1. The PDE4 inhibitor roflumilast is not a failure.

1069. The PDE4 inhibitor roflumilast should not be considered a failure. Knowles Tr. 220:16-20; Knowles Tr. 254:10-11; PDX4-14.

1070. Roflumilast is a PDE4 inhibitor suitable for use as a pharmaceutical composition. Page 787:16-18; Knowles Tr. 254:12-18.

1071. Roflumilast was effective, minimized side effects, and was approved by the FDA. Knowles Tr. 254:10-22.

1072. The oral PDE4 inhibitor roflumilast obtained FDA approval in 2011, prior to Otezla® (apremilast) obtaining FDA approval. Page Tr. 787:9-15; Schafer Tr. 169:3-9; Schafer Tr. 168:11-14.

1073. Otezla® (apremilast) did not obtain FDA approval until 2014. Schafer Tr. 169:3-9; Schafer Tr. 168:11-14.

2. None of the compounds Dr. Knowles discussed as being discontinued were apremilast, let alone stereomerically pure apremilast and Dr. Knowles was unable to provide the reasons why many of the compounds he discussed were discontinued.

1074. Dr. Knowles opined that, by October 1999, the development of six PDE4 inhibitors had been discontinued (Knowles Tr. 221:17-225:14; PDX4-15) and that they were failures given that they did not obtain FDA approval. Knowles Tr. 243:23-244:8.

1075. However, for two of those six compounds (filaminast and D-4418) Dr. Knowles discussed as being discontinued by October 1999, the reason these compounds were discontinued was not stated. Knowles Tr. 225:9-14; Knowles Tr. 248:8-11; PDX4-15.

1076. None of the six compounds discussed by Dr. Knowles as being discontinued by October 1999 were apremilast. Knowles Tr. 243:24-244:13; PDX4-15.

1077. None of the six compounds discussed by Dr. Knowles as being discontinued by October 1999 referred to stereomerically pure apremilast. Knowles Tr. 243:23-244:3; Knowles Tr. 244:13-15; PDX4-15.

1078. None of the six compounds discussed by Dr. Knowles as being discontinued by October 1999 were described as potentially indicated to treat psoriasis. Knowles Tr. 243:23-244:3; Knowles Tr. 244:16-18; PDX4-15.

1079. Dr. Knowles also opined that, by March 2002, the development of seven other PDE4 inhibitors had been discontinued. Knowles Tr. 225:15-226:25; PDX4-16.

1080. However, for five out of those seven compounds (tibenelast, D-22888, V-11294A, Ym-976, and BAY-19-8004) Dr. Knowles discussed as being discontinued by March 2002, Dr. Knowles noted that the reason these compounds were discontinued were not stated. Knowles Tr. 226:19-25; Knowles Tr. 248:12-18; PDX4-16.

1081. None of the seven compounds discussed by Dr. Knowles as being discontinued by March 2002 were apremilast. Knowles Tr. 248:12, 22-24; PDX4-16.

1082. None of the seven compounds discussed by Dr. Knowles as being discontinued by March 2002 referred to stereomerically pure apremilast. Knowles Tr. 248:12, 22-25, 249:1-3 PDX4-16.

1083. None of the seven compounds discussed by Dr. Knowles as being discontinued by March 2002 were described as potentially indicated to treat psoriasis. Knowles Tr. 248:12; Knowles Tr. 249:5-7; PDX4-16.

3. Drug development programs may be discontinued due to reasons other than shortcomings in a drug candidate's properties.

1084. Moreover, that development of certain PDE4 compounds was eventually discontinued does not demonstrate failure of others. The reasons why a drug development program would be halted may be complex and are not always simply because a drug has shortcomings concerning safety and/or efficacy. Page Tr. 741:23-742:15

1085. Commercial reasons can be a factor into a company's decision whether to continue or discontinue a drug development project. Knowles Tr. 248:1-6.

1086. A company might discontinue a drug development program due to lack of necessary finances, or a company merging, which results in management changing priorities. Page Tr. 742:16-743:2.

1087. Additionally, companies may discontinue a drug development program for commercial reasons, even if the candidate drug showed promising results; one example of this situation would be if the candidate drug is no better than the products already on the market or soon to be entering the market. Page Tr. 743:23-744:7.

4. Many PDE4 inhibitors had entered clinical trials in humans as of the priority date.

1088. Dr. Knowles also implied that a failure would be found if a PDE4 inhibitor identified in step one of his drug development cascade "fail[ed] to reach clinical studies in humans." Knowles Tr. 209:23:210-3. If the foregoing was the standard to be used in determining whether a compound was a failure, then many PDE4 inhibitors should not be found to be failures given that other compounds entered clinical studies in humans as of the priority date.

1089. In 1999, the PDE4 inhibitor roflumilast was in phase 2 and 3 clinical studies in humans. PDX4-12; JTX-142.4-5.

1090. In 1999, the PDE4 inhibitor cilomilast was in phase 3 clinical trials in humans. PDX4-12; JTX-67.5.

1091. In addition, Dr. Knowles discussed five compounds that were in phase 1 clinical studies (CI-1018, T-440, YM-58997, D-22888, and arofylline), and three compounds that were in phase 2 clinical studies (CDC-801, V-11294A, and atizoram), as of October 1999. See Knowles Tr. at 213:23-214:2; PDX4-12.

1092. For the foregoing reasons, Amgen (and Dr. Knowles) have failed to present persuasive evidence of any failures of others.

D. There is No Evidence of Unexpected Results that Supports the Non-Obviousness of the Asserted Claims of the '638 and the '536 Patents.

1. There is no evidence of unexpected results based on comparison of apremilast to cilomilast, based on their therapeutic indices in Celgene's Ferret Study.

1093. Dr. Knowles conclusorily testified that a POSA would not have expected a 31-fold improvement in the therapeutic index for apremilast as compared to cilomilast in Celgene's

Ferret Study. Knowles Tr. 236:14-22. Dr. Knowles also offered a conclusory opinion that "apremilast is only apremilast if it's essentially pure." Knowles Tr. 243:3-6.

1094. As an initial matter, cilomilast is not the closet prior art to the asserted claims of the '638 and '536 patents. *See* Gribble Tr. 590:14-19 (noting that the asserted claims of the '638 patent is anticipated by the '358 patent; Gilmore Tr. 871:13-23 (noting that the asserted claim of the '536 patent is anticipated by the '358 patent).

1095. Dr. Knowles relied on confidential data that a POSA would not have had access to in discussing the therapeutic indices of apremilast and cilomilast. Knowles Tr. 235:7-16; Knowles Tr. 255:24-256:10; PTX-374; JTX-118.

1096. Furthermore, apremilast's therapeutic index of 12 in Celgene's Ferret Study does not support unexpected results, due to the problems discussed with this measurement above. DFF ¶¶ 1001-1048.

1097. To even potentially reach a determination that apremilast was superior to cilomilast, a POSA would need additional data from other experiments that looked at side effects other than emetic episodes, to properly determine the therapeutic windows of apremilast and cilomilast. Page Tr. 738:10-17.

1098. A POSA would not determine that apremilast was superior to cilomilast based solely on a 31-fold difference in their therapeutic indices in Celgene's Ferret Study. Page Tr. 738:10-15.

2. There is no evidence of unexpected results based on Dr. Knowles's comparison of apremilast to the racemic mixture (Example 12 of the '358 patent) based on only two data points.

1099. Dr. Knowles compared the PDE4A4 ratio and potency data in a mouse model to argue that apremilast exhibited unexpected results over the racemic mixture (i.e., Example 12). Knowles Tr. 237:2-15 (discussing the PDE4A4 ratios) and Knowles Tr. 239:3-240:8 (discussing

potency data). However, this data does not demonstrate that apremilast exhibited unexpected results as compared to Example 12, for the reasons discussed below.

a. PDE4A4 ratio

1100. Dr. Knowles relied on Dr. Schafer's testimony that "apremilast had a PDE4A4 ratio that was much lower than that of Example 12." Knowles Tr. 237:6-9. Dr. Knowles stated that apremilast exhibited an 11-fold improvement in its PDE4A4 ratio, as compared to Example 12. Knowles Tr. 232:20-233:2; PDX4-17.

1101. The document disclosing the PDE4A4 ratios discussed by Dr. Knowles was confidential Celgene information. Knowles Tr. 256:25-257:13; 257:25-258:19; JTX-208.1, 14. The PDE4A4 ratio discussed by Dr. Knowles was an internal Celgene calculation that was not known to the person of ordinary skill in the art. Knowles Tr. 257:25-258:19; JTX-208.14.

1102. Dr. Knowles conclusorily testified that the lower PDE4A4 ratio of apremilast would have been unexpected, simply stating that "[t]here was no data to provide a POSA or anyone else to think that that might be the result." Knowles Tr. 237:10-15.

b. Potency in Celgene's *in vivo* mouse model

1103. Dr. Knowles testified that apremilast exhibited a 20-fold improvement in potency *in vivo* in a mouse model, as compared to Example 12, when measuring inhibition of TNF-α. Knowles Tr. 238:6-16; 239:3-7; PDX4-17-18. Dr. Knowles conclusorily testified that the POSA would not have expected a 20-fold difference in potency between apremilast and Example 12. Knowles Tr. 240:11-13.

1104. Dr. Knowles relied on Celgene's confidential internal data which would not have been available to a POSA when comparing the potency data for apremilast and Example 12. Knowles Tr. 239:3-7; 240:9-10; Knowles Tr. 262:2-13; JTX-114.

1105. The potency data from Celgene's *in vivo* mouse model would have been a test done early in the development of a drug. Knowles Tr. 263:2-8.

1106. The potency data in Celgene's *in vivo* mouse model would not predict a dose range of a compound which could be effective in human studies. Page Tr. 740:7-15.

1107. A POSA would not rely on potency data alone to determine that apremilast was unexpectedly superior to Example 12. Page Tr. 739:15-740:6.

1108. The potency data discussed by Dr. Knowles is not relevant to the dose-limiting toxicity of nausea, emesis, or diarrhea. Knowles Tr. 263:9-17.

c. Example 12 had advanced into clinical studies in humans.

1109. Example 12 was also named "7085" or "CC-7085" (Schafer Tr. 139:22-24), "CC-17085" (Knowles Tr. 259:14-19), and CDC-998 (Knowles Tr. 1738:13-15; Knowles Tr. 1738:18-20).

1110. CC-7085 is a racemic mixture, and apremilast is one of the enantiomers that makes up that racemic mixture. Schafer Tr. 143:22-144:1.

1111. Example 12 (CC-7085) was advanced into three phase 1 clinical trials in humans. Schafer Tr. 162:20-163:1; *see also* PDX3-2; JTX-208.70.

1112. Example 12 (CC-17085) was described by Celgene as a compound with increased potency and improved low affinity/high affinity ratio. Knowles Tr. 258:21-259:19; JTX-208.39.

1113. In a human clinical study involving Example 12, Example 12 was found to be well tolerated. Knowles Tr. 260:16-25;

1114. In a human clinical study involving Example 12, most adverse events were mild. Knowles Tr. 261:1-4; JTX-208.70.

1115. In a human clinical study involving Example 12, there were no serious adverse events. Knowles Tr. 261:1-7; JTX-208.70.

1116. In a human clinical study involving Example 12, none of the adverse events were suspected to be treatment-related. Knowles Tr. 261:8-10; JTX-208.70.

1117. In a human clinical study involving Example 12, no clinically relevant changes were observed for any of the vital sign observations, laboratory safety evaluations, or 12-lead ECG recordings. Knowles Tr. 261:11-19; JTX-208.70.

1118. Dr. Knowles described a six step evaluation process for a PDE4 inhibitor or a "cascade of different assays" (Knowles Tr. 202:16-23), with those steps being: (1) enzyme assays; (2) cellular assays; (3) *in vivo* animal efficacy and acute tolerability models (including therapeutic index); (4) assessments of physicochemical properties and animal pharmacokinetics; (5) chronic safety studies; and (6) clinical studies in humans. Knowles Tr. 202:8-210:7; PDX4-6. Dr. Knowles noted that the enzyme assays described in this cascade "would be relatively quick and inexpensive methods to determine" the initial ability of compounds to inhibit PDE4. Knowles Tr. 202:204:12.

1119. When a drug has entered phase 1, phase 2, or phase 3 clinical studies, that drug would have passed through each of steps one through five in Dr. Knowles's drug development cascade. Knowles Tr. 1722:2-24.

1120. Human clinical studies of Example 12 would have occurred in step six of the six step drug development cascade or evaluation progress of PDE4 inhibitors described by Dr. Knowles. Knowles Tr. 263:18-22; PDX4-6.

1121. Therefore, Example 12 would have shown results satisfactory to Celgene through steps 1-5 of the drug development cascade or PDE4 evaluation process. Knowles Tr. 263:23-264:8; PDX-4-6.; Knowles Tr. 1730:12-1731:14.

1122. For the foregoing reasons, Amgen (and Dr. Knowles) have failed to present persuasive evidence of any failures of others.

E. There Was No Skepticism Regarding Apremilast's Structural Features.

1123. A POSA would not have been skeptical of apremilast. (Gribble Tr. 612:16-613:6; DDX2-52.).

1124. The only portion of apremilast that is in common with thalidomide is the left-side phthalimid ring and the rest is different. (Gribble Tr. 612:16-613:6; DDX2-52; Davies Tr. 1420:11-1421:3.)

1125. The toxicity of thalidomide as a teratogen is related to the acidic hydrogen on the chiral carbon that causes thalidomide to racemize. (Gribble Tr. 616:12-613:6; DDX2-52.)

1126. Apremilast does not have an acidic hydrogen on its chiral carbon and does not, and would not be expect to, racemize. (Gribble Tr. 612:16-613:6; DDX2-52.)

1127. Apremilast is more structurally different than similar to thalidomide. (Gribble Tr. 612:16-613:6; DDX2-52.)

1128. Celgene's 2004 memo regarding a meeting with FDA explains that apremilast has a chiral center that is not acidic, and thus not racemizable like the chiral center found in thalidomide. (Gribble Tr. 615:6-17; DDX2-54; JTX-281.3.)

1129. FDA was satisfied with Celgene's descriptions distinguishing the structural characteristics of apremilast from thalidomide. (Gribble Tr. 615:6-17; DDX2-54; JTX-281.3.)

1130. By the time of the '358 patent, thalidomide was approved for use in treating leprosy. (Gribble Tr. 716:23-717:9; Davies Tr. 1421:24-1422:3.)

1131. By the time of the '358 patent, thalidomide analogs were being studied as potential new drugs. (Gribble Tr. 613:8-19; DDX2-53; Davies Tr. 1421:24-1422:3, 1427:21-1428:2.)

1132. A POSA would have been interested in developing thalidomide analogs that lack an acidic hydrogen on the chiral carbon. (Gribble Tr. 613:16-614:2; DDX2-53.)

1133. By the time of the '358 patent, people in the art were aware of the side effects of thalidomide. (Davies Tr. 1428:3-6.)

1134. Marriott 2001 states that "[t]he immunomodulatory drug thalidomide has been shown to be clinically useful in a number of conditions, including various immunological disorders and cancers." (Davies Tr. 1423:6-10; JTX-66.2)

1135. Marriott 2001 states that "thalidomide is now established as an effective immunomodulatory and anti-inflammatory drug." (Davies Tr. 1424:11-13; JTX-66.2)

1136. Marriott 2001 states that "[i]n particular, thalidomide has shown potential for the treatment of a range of conditions, including rheumatoid arthritis." (Davies Tr. 1425:10-13-; JTX-66.3)

1137. Marriott 2001 states "it would seem likely that novel compounds designed using thalidomide structure as a lead would allow optimization of its immunological and anti-cancer properties while decreasing its side effects." (Davies Tr. 1430:21-25, 1431:7-14; JTX-66.4.)

1138. Thalidomide was known as a racemic mixture and it was suggested to separate the enantiomers in order to avoid the side effects seen with the racemic mixture. (Davies Tr. 1429:11-18; JTX-66.3.).

F. There Is No Long-Felt Unmet Need Met By Apremilast.

1200. Dr. Alexis opined that there was a long-felt but unmet need that existed prior to and was satisfied by apremilast for a treatment for moderate plaque psoriasis that was safer than what existed prior and lacked potential barriers to adherence seen with other Treatments. Alexis Tr. 266:6-21. However, there is no evidence of such long-felt unmet need nor was any such need met by Otezla® or the claimed inventions of the '536 or '638 patent.

1201. Asserted claim 6 of the '536 patent requires "[a] method of treating psoriasis" in a patient by administering 10 mg to about 200 mg per day of stereomerically pure apremilast. JTX-7.20-21. Simply put, the asserted claim of the '536 patent requires a method of treating psoriasis {not limited to mild, moderate or severe psoriasis) by administering apremilast. *Id.*; *see also* Gilmore Tr. 866:23-867:2.

1202. Asserted claims 3 and 6 of the '638 patent require a "pharmaceutical composition" of stereomerically pure apremilast that is "suitable for oral administration to a patient" or "dosed from 10 mg to 200 mg." JTX-3.21.

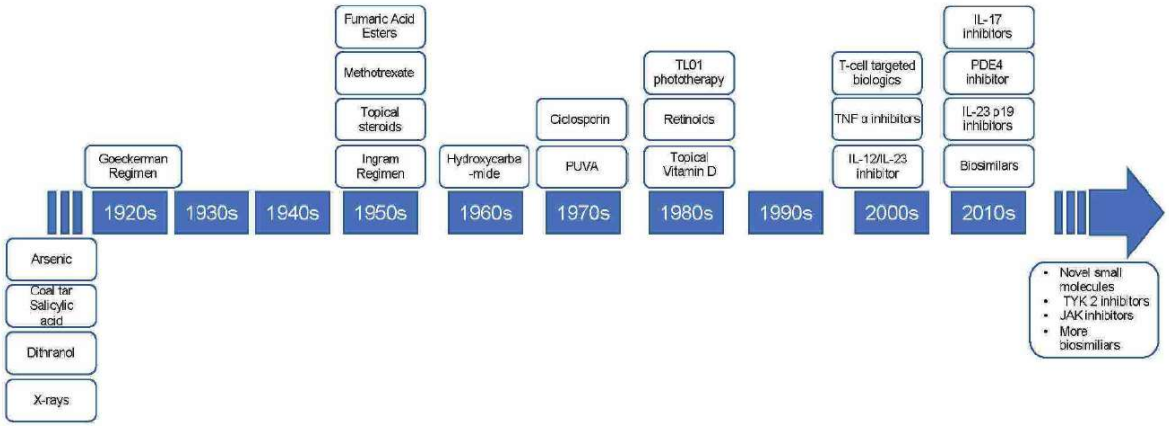
1203. The asserted claim of the '536 patent does not require that the method of treatment is a "safer" treatment for moderate plaque psoriasis, or that it "does not present the same potential barriers to adherence of other treatment options." Gilmore Tr. 866:23-867:2; JTX-7.20-21.

1204. The asserted claims of the '638 patent do not require that the pharmaceutical composition be a "safer" treatment for moderate plaque psoriasis, indeed there are no method of treatment claims in the '638 patent, nor do the claims require that the pharmaceutical composition "not present the same potential barriers to adherence of other treatment options." JTX-3.23.

1205. Indeed, none of these characteristics are described in the specifications of the '536 or '638 patents as being allegedly novel aspect of the claimed inventions over the prior art. JTX-3.6-21; JTX-7.6-20.

1206. Apremilast did not satisfy any long-felt need in the treatment of patients suffering from psoriasis (or psoriatic arthritis) that was not met by other existing therapies. Gilmore Tr. 901:7-9, 878:18-879:5.

1207. First, even before the March 2002 priority date of the '536 and '638 patents and long before Otezla® was approved by the FDA in 2014, there were several existing therapies that were effective and safe for treating psoriasis, including topical therapies such as steroids and systemic therapies such as methotrexate, ciclosporin, acitretin, and certain TNFα inhibitors. Gilmore Tr. 826:24-827:10, 878:18-23, 888:5-12; DTX-372.2 (graphic copied below).



1208. "Psoriasis is a chronic skin disease that, although usually not life-threatening causes tremendous morbidity and has not cure." DTX-215.1; *see also* Gilmore Tr. 820:21-23, 821:25-822:3; Alexis Tr. 276:14-277:14, 278:22-25. The choice of treatment depends on the extent and severity of the disease and the preferences and treatment goals of the patient. Gilmore Tr. 824:25-8:25-11.

1209. Severity of disease is measured using the Psoriasis Area and Severity Index (also known as the PASI score), "which takes into account the size of the area involved, redness, thickness, and scaling®" and can be used to categorize a patient's psoriasis as mild, moderate, or severe. DTX-217.1-2; Gilmore Tr. 822:25-823:3, 823:9-15. A patient with moderate disease is still "pretty extensive" with a "significant amount of itching and scaling." Gilmore Tr. 823:22-23, 824:1-3. The quality of life for a patient suffering from psoriasis can be "quite poor" and a

person suffering from moderate psoriasis can still have "major, major issues." Gilmore Tr. 824:7-21.

1210. The first line of treatment for patients with more mild disease was topical treatment, which is still used today. DTX-372.2; Gilmore Tr. 827:5-6; Alexis Tr. 315:5-11. For patients with more extensive disease, systemic therapy is usually warranted. DTX-372.2; Gilmore Tr. 827:7-10.

1211. One such oral systemic treatment for psoriasis is methotrexate, which has been around for decades. DTX-372.2; Gilmore Tr. 827:5-10, 878:18-23. Methotrexate is a folic acid antagonist that "is an effective therapy for selected patients with psoriasis" and "has been the standard of care in the clinical setting for over 50 years. DTX-217.5; DTX-367.2. Even today methotrexate "remains the most commonly used treatment for psoriasis." DTX-367.2. Indeed, both Defendants' and Amgen's clinical experts prescribe methotrexate to this day. Gilmore Tr. 827:5-10, 882:1-3; Alexis Tr. 314:22-315:1.

1212. Biologics (also known as TNFα inhibitors) were available and effective for systemically treating psoriasis before the claimed inventions in 2002 and Otezla® was approved in 2014. DTX-372.2; Gilmore Tr. 827:22-24, 828:9-10; 888:5-12; Alexis Tr. 279:5-6. Biologics are "a subgroup of drugs comprised of large complex protein molecules including monoclonal antibodies and receptor fusion proteins." DTX-372.4; Gilmore Tr. 883:20-24. Biologics are administered parenterally. Gilmore Tr. 884:18-22; Alexis Tr. 284:5-6.

1213. Biologics were revolutionary and "transformed the standard of care for patients," particularly those with moderate to severe disease. DTX-372.8; Gilmore Tr. 827:11-828:8, 882:23-883:4, 883:25-884:7. "The injectable biologic agents, specifically the TNF-α inhibitors, completely revolutionized [physicians'] approach to the treatment of patients with [psoriasis].

The efficacy of these medications was unheard of in relation to the outcomes we could expect from prior therapies that were available." Gilmore Tr. 828:3-8. Biologics were also attractive because they had fewer side effects. *See, e.g.*, DTX-372.5-7. Before 2002, the first generation of biologics were on the market, including Enbrel® and Remicade®. Gilmore Tr. 828:9-10. By the time Otezla® was approved in 2014, there were several biologic therapies that had been approved by the FDA for the treatment of psoriasis, including: Enbrel® (approved in 2004 for psoriasis); Remicade® (approved in 2006 for psoriasis); Humira® (approved in 2008 for psoriasis); and Stelara® (approved in 2009 for psoriasis). Gilmore Tr. 888:9-12.

1214. The benefit of using biologics is that they are designed to "target specific components of the immune system that are involved in psoriasis pathogenesis." DTX-372:1, 8; Gilmore Tr. 883:13-24. "Many of these molecules interfere with the TNFα pathway that was identified as being particularly relevant in the development of psoriatic disease." Gilmore Tr. 882:16-18. Thus, biologic drugs are more effective in treating psoriasis than other therapies, including methotrexate and later Otezla®. Gilmore Tr. 881:20-22.

1215. The first generation of biologic drugs to show a market improvement in efficacy were TNFα inhibitors, such as Enbrel®, Remicade®, and Humira®, which directly inhibit TNFα production by inflammatory cytokines. DX-372.5; Gilmore Tr. 828:9-10; 882:19-21. The PASI scores associated with these drugs showed a significant measure of improvement of disease severity in clinical trials. Gilmore Tr. 887:16-24.

1216. A PASI-75 score in a clinical trial refers to a 75 percent improvement in the disease severity measured at a certain endpoint (e.g., 12 or 16 weeks) when compared to the patient's PASI score at the beginning of the trial. Gilmore Tr. 886:21-887:5; Alexis Tr. 319:11-14, 320:10-22.

1217. The first generations of biologics had the following PASI-75 scores from clinical trials:

Drug	Approval (psoriasis)	PASI-75 (%)
Enbrel®	2004	47% 46%
Remicade®	2006	80% 75% 88%
Humira®	2008	71% 78%
Stelara®	2009	66% 76%

Gilmore Tr. 887:19-24, 888:5-12; Alexis Tr. 327:16-328:5, 331:1-8; DTX-372.4-8.

1218. Even after Otezla® became commercially available, there was a continued interest in further developing biologic drugs as more became known about the etiology of psoriasis, including Cosentyx®, Siliq®, Tremfya®, and Taltz®. *See, e.g.*, DTX 372.6. For the first time, significant numbers of patients achieved PASI-90 and PASI-100 with treatment using these newer biologics as shows by the below data from clinical trials:

Drug	Approval (psoriasis)	PASI-75 (%)	PASI-90 (%)	PASI-100 (%)
Cosentyx® (300 mg)	2015	82% 76% 75% 87%	59% 54%	
Siliq®	2017	83% 86% 85%		42% 44% 37%
Tremfya®	2017	91% 83%	73% 64%	
Taltz®	2018	89% 90% 87%	71% 71% 68%	35% 40% 38%

Gilmore Tr. 887:9-15; Alexis Tr. 333:24-334:10, 335:2-20, 337:21-338:1, 339:1-19, 340:21-341:8, 337:21-338:1, 342:5-17, 343:4-7; DTX-372.6.

1219. Thus, to the extent there was any alleged long-felt need for the treatment of psoriasis before apremilast, it was met by the use of existing oral, systemic therapies, such as methotrexate, and first/second generation biologic drugs. Gilmore Tr. 878:15-879:2. Moreover, to the extent that such need still existed after Otezla®, it was met by the new generation of biologic drugs such as Cosentyx®, Siliq®, Taltz®, and Tremfya®, which have shown the ability to achieve 90% or even 100% clearance of psoriatic plaques and lesions. Gilmore Tr. 882:23-883:4.

1220. Because biologic treatments provide vastly superior efficacy and faster onset of relief, issues like needle phobia or potential side effects did not deter many patients from pursing treatment with a biologic drug before (or even after) apremilast. Gilmore Tr. 884: 18-885:22; 894:7-20. Even for the small subset of patients who did have needle phobia, traditional, oral therapies such as methotrexate were (and still are) always an option. Gilmore Tr. 897:21-23. Furthermore, many biologics use an injection device where the patient does not see a needle, and those administered via syringe and needle are generally administered in the physician's office with minimal frequency, such as four times a year. Gilmore Tr. 885:1-20; Alexis Tr. 325:1-326:2.

1221. Second, apremilast did not satisfy any alleged unmet need. There is currently no cure for psoriasis. Gilmore Tr. 820:23; Alexis Tr. 278:22-25. Thus, the goal of any treatment is to decrease the severity and extent of clinical symptoms and increase quality of life. Gilmore Tr: 824:22-825:11.

1222. While apremilast has been shown to reduce the severity of psoriasis in clinical trials, it is not more effective than conventional oral therapies, such as methotrexate, and is much less effective than biologics. Gilmore Tr. 878:18-879:2, 888:20-889:1 ("Otezla® is not like others [namely, biologic treatments with PASI-75, 90, and 100 scores] and has significantly less effectiveness than some of the other choices we have that can significantly improve a patient's psoriatic disease."); Alexis Tr. 336:10-15, 342:24-343:7 (regarding higher PASI scores for biologics as compared to Otezla®).

1223. Scientific literature recognizes the relative equivalency in efficacy of apremilast and methotrexate. DTX-367.1; DTX. 377.1; Gilmore Tr. 879:9-13. Apremilast's efficacy in treating moderate to severe psoriasis is similar to methotrexate and offers no particular advantages in terms of the ability to alleviate a patient's clinical symptoms. DTX-367.1; DTX-377.1; Gilmore Tr. 880:9-11, 881:17-22. One study reported "[n]o statistically significant difference was found between apremilast and methotrexate in PASI 75." DTX-367.1; see also Gilmore Tr. 879:19-22, 880:3, 8-25. Other literature reported that with regard to apremilast, "[e]fficacy in psoriasis is probably equivalent to methotrexate but less than that of monoclonal antibody inhibitors of tumor necrosis factor (TNFi)." DTX-377.1; see also Gilmore Tr. 881:6-8, 16-22. Dr. Gilmore testified that the conclusions in the scientific literature were consistent with what she sees in practice, namely that her "patients treated with methotrexate and apremilast show about the same amount of improvement." Gilmore Tr. 881:23-882:3.

1224. Further, apremilast is much less effective than biologics, including those that pre-dated Otezla®, in clearing psoriatic lesions. Gilmore Tr. 878:24-879:2. Only 28.8% to 33.1% of psoriasis patients in phase III studies of Otezla® achieved a 75% or greater reduction in their

PASI score compared with baseline. JTX-110.12; Gilmore Tr. 878:24-879:1; Alexis Tr. 322:6-14.

1225. The following shows the PASI scores from clinical trials of Otezla® compared to biologics that pre- and post-dated Otezla®'s launch.

Drug	Approval (psoriasis)	PASI-75 (%)	PASI-90 (%)	PASI-100 (%)
Enbrel®	2004	47% 46%	—	—
Remicade®	2006	80% 75% 88%	—	—
Humira®	2008	71% 78%	—	—
Stelara®	2009	66% 76%	—	—
Otezla®	2014	33.1% 28.8%	—	—
Cosentyx® (300 mg)	2015	82% 76% 75% 87%	59% 54%	—
Siliq®	2017	83% 86% 85%	—	42% 44% 37%
Tremfya®	2017	91% 83%	73% 64%	—
Taltz®	2018	89% 90% 87%	71% 71% 68%	35% 40% 38%

Gilmore Tr. 888:17-19.; Alexis Tr. 327:16-328:5, 331:1-8, 333:24-334:10, 335:2-20, 337:21-338:1, 339:1-19, 340:21-341:8, 337:21-338:1, 342:5-17, 343:4-7; DTX-372.4-8; JTX-110.12.

1226. Dr. Gilmore testified, regarding the data in the above chart, that: "This chart allows us to put into perspective the type of efficacy we can expect and consider for treating a patient with Otezla versus other options that we have for therapy on the market. It shows basically that Otezla is not like the others and has significantly less effectiveness than some of

the other choices we have that can significantly improve a patient's psoriatic disease. Gilmore Tr. 888:20-1. Apremilast was not a revolutionary or transformative drug but simply one of many drugs in the arsenal of physicians. Gilmore Tr. 876:21-23 (Otezla® is "one of a number of medications that I prescribe within my armamentarium").

1227. Dr. Alexis testified that efficacy is important, and it was not his opinion that apremilast offers the best efficacy of any treatment for plaque psoriasis. Alexis Tr. 303: 20-22, 344:11. He recognized that prescribing treatment for psoriasis requires an assessment of many factors, and apremilast is not the solution for everyone. Alexis Tr. 303:25-304:8 ("When I prescribe a drug for plaque psoriasis or any other condition, I have to take into consideration every aspect of the drug. That includes efficacy, but it also includes safety. It also includes tolerability. It might also include lifestyle factors for the patient. Does this align with the patient's lifestyle and their own preferences? So it's impossible to isolate just one attribute of a drug. I have to take into account the entire package.").

1228. In addition, apremilast's safety profile is not more favorable than any other available therapy for moderate to severe psoriasis. Gilmore Tr. 879:3-5; 890:1-891:19. Apremilast is associated with significant gastrointestinal-related side effects, such as diarrhea, cramping, and nausea. Id. at 877:19-20, 890:3-11; JTX-110.3. The Warnings and Precautions section of the Otezla® Label explain that "[t]here have been postmarketing reports of severe diarrhea, nausea, and vomiting associated with the use of OTEZLA." JTX-110.3; Gilmore Tr. 890:6-11. "Post-marketing reports are safety events that are reported after the drug is approved." Alexis Tr. 1858:17-18. The Otezla® label further provides that "patients who reduced dosage or discontinued OTEZLA generally improved quickly." JTX-110.3; Gilmore Tr. 890:6-11.

1229. Many physicians do not prescribe Otezla® according to the label and will typically titrate the dose over four weeks because a large percentage of patients have difficulty tolerating Otezla® on a six-day titration schedule. *See, e.g.,* Gilmore Tr. 876:24-877:20; 948:4-11; JTX-98; JTX-99; JTX-100. Indeed, Celgene's internal documents reported that advisory boards of physicians and key opinion leaders were complaining about GI tolerability issues with regard to Otezla® and at one point Celgene considered changing the titration schedule for Celgene due to the high incidence of GI side effects. See JTX-98.4, 11 (discussing GI tolerability of Otezla®); JTX-99; JTX-100.25-26 (showing that Celgene considered changing the titration schedule for Otezla®).

1230. Dr. Gilmore testified "it was important to change the titration because of the high proportion of patients who were unable to continue with therapy." Gilmore Tr. 877:13-15. She estimated that 40-50% of patients to whom she prescribed Otezla® chose not to stay on the therapy when she provided the starter packed because "it really wasn't well-tolerated primarily because of GI side effects: nausea, vomiting and diarrhea." Gilmore Tr. 877:15-20.

1231. Patients who receive apremilast for moderate to severe psoriasis are already suffering in their daily lives due to the symptoms and discomfort associated with their disease. Gilmore Tr. 823:22-824:21; Alexis Tr. 285:2-23. Their social interactions and occupations are often impacted because they are self-conscious and embarrassed by the visible plaques and because it can elicit questions and concerns from others. Gilmore Tr. 823:22-824:21; Alexis Tr. 285:2-23. The significant gastrointestinal side effects associated with Otezla®, such as diarrhea, are not welcome side effects by patients who already have a poor quality of life. Gilmore Tr. 891:5-19 (Patients "coming in with a skin disease, sometimes a very significant skin disease, and I'm giving them the medication [Otezla®] that then gives them a GI disease as well. So this is

not an improvement in their quality of life, which is often the goal that they're seeking in their psoriasis treatment").

1232. The Otezla® label also warns that "[t]reatment with OTEZLA is associated with an increase in adverse reactions of depression." JTX-110.3. The Otezla® label provides clinical data showing that patients taking Otezla® had a higher incidence of depression than placebo. *Id*. The fact that a warning regarding the risk of depression is included on the label indicates that it is a side effect associated with Otezla® that should be taken seriously. Gilmore Tr. 890:12-19. Dr. Gilmore testified that she has observed the types of side effects discussed in the label, "particularly GI side effects and as well the risks of depression," and that she has "had patients who have decided not to proceed with therapy when reading about the risk of worsening depression with this drug." Gilmore Tr. 890:23-891:2.

1233. Thus, apremilast does not satisfy a need for a medication that is without barriers. In addition to significant gastrointestinal and mental health side effects, "Otezla is dosed twice daily so the patient is making a commitment to taking medications morning and night." Gilmore Tr. 896:23-897:4. Apremilast is dosed more frequently than the similarly efficacious methotrexate, which is dosed orally once weekly, and much less frequently than biologics which are dosed ranging from weekly, monthly, and in some cases quarterly. Gilmore Tr. 896:13-22.

1234. That Otezla® does not have a black box warning or require lab monitoring does not satisfy a long-felt need for a safer drug or imply that it is safer than methotrexate or biologics. Gilmore Tr. 892:20-896:10. Methotrexate, ciclosporin, acitretin, and the various biologics are all FDA approved as safe and effective for administration to humans. Gilmore Tr. 892:1-12; Alexis Tr. 296:22-297:3. The incidence of many of the potential side effects of methotrexate and biologics is "very low," and Dr. Gilmore testified that she has seen very little

incidence of patients who are declining a treatment because it requires lab monitoring. Gilmore Tr. 894?9-895:8; 896:7-10. "There are pros and cons to using all medications, whether you're treating psoriasis or any other condition. It is a common practice for a physician to go through the risk-benefit profile along with a patient to determine the right course of therapy. We understand that medications have side effects and we take measures to makes sure that patients don't display those side effects and don't experience those side effects. So if we need to monitor certain lab work, we do that. If we need to ensure a dosing schedule helps to prevent issues with skin atrophy … associated with corticosteroid, we do that. So certainly the choice of treatment to give to which patient is going to be pretty individualized and require a lot of counseling and education." Gilmore Tr. 893:2-15.

1235. Apremilast is not useful for patients with severe, debilitating symptoms of psoriasis, due to its limited efficacy as compared to biologics, and is more likely to be prescribed for patients with mild to moderate symptoms of psoriasis—patients who are less likely to tolerate and continue to take apremilast in light significant gastrointestinal-related adverse events, particularly if experienced on a daily basis. *See, e.g.*, Gilmore Tr. 878:1-8, 888:20-889:1; DTX 372; JTX-98; JTX-99; JTX-100; JTX-110. Dr. Gilmore testified that "Otezla® really was not a major factor in changing my approach to treatment of patients. It is a medication that I use sometimes for my patients, but it's one of . . . many choices that I have and one of several oral therapies form which I can choose. So I feel that, you know, given the side effect, that has really, unfortunately, limited my ability to use the medication so it's really not fulfilling an – an unmet need." Gilmore Tr. 878:1-8.

G. Apremilast Does Not Demonstrate "Clinical Success."

1236. There is no evidence that apremilast has obtained substantial success in the clinic as a widely-prescribed treatment for plaque psoriasis or moderate plaque psoriasis for four main

reasons: (1) biologics are more efficacious and require less frequent dosing; (2) methotrexate is still commonly prescribed, has similar efficacy to apremilast, is less expensive, and requires less frequent dosing; (3) Otezla® is associated with significant side effects that often lead to discontinuation; and (4) marketing of Otezla® has influenced prescribing practices. Gilmore Tr. 897: 17-898:4; 901:7-9. Dr. Alexis provided no data other than anecdotes to support his argument of "clinical success" of Otezla®. *See*, *e.g.*, Alexis Tr. 305:10-306:24.

1237. First, in addition to the improved efficacy discussed at length above, some patients also find biologics preferable because they are dosed much less frequently than Otezla® twice daily dosing. Gilmore Tr. 897:2-4, 897:17-898:4. *See also* Alexis Tr. 326:15-25,

1238. For example, Stelara® is dosed every three months, Humira® is dosed once every other week, and Enbrel® is dosed once weekly. Gilmore Tr. 896:13-19. *See also*, Alexis Tr. 326:10-20, 329:13-25. Cosentyx® is dosed every week from weeks 0 through 4 and then every four weeks. Alexis Tr. 332:3-8. Tremfya® is dosed at week 0, week 4 and then every eight weeks. DTX-363.2; Alexis Tr. 337:14-16. Siliq® is dosed weekly for the first three weeks, and then every two weeks. JTX-222:2; Alexis Tr. 338:10-21. Taltz® is dosed every two weeks for the first 12 weeks and then once a month after week 12. JTX-157.1; Alexis Tr. 340:9-16. Ilumya® is dosed at week 0, 4 and then every three months after week 12. PTX-419.1; Alexis Tr. 342:2-4.

1239. Second, patients and physicians may find Methotrexate preferable to apremilast because it has similar efficacy, is available as a generic (and therefore is less expensive) and is dosed only once weekly (as opposed to twice a day for Otezla®). Gilmore Tr. 897:17-24; Alexis Tr. 317:23-318:2, 15-17.

1240. Third, because apremilast is associated with significant gastrointestinal-related side effects, a significant number of patients have difficulty tolerating Otezla®. Gilmore Tr. 877:3-7, 13-20; 890:20-891:13; Alexis Tr. 1858:3-6 (30 to 50 percent of Dr. Alexis' patients experience GI adverse events with Otezla). About 40-50% of patients decide to discontinue treatment because of their level of discomfort. *Id*. As such, Otezla® has not achieved "substantial success" in the clinic, particularly when compared against other available treatment options.

1241. Finally, Amgen's and Celgene's marketing efforts for Otezla® would have influenced physicians to prescribe Otezla® over other treatments. Physicians often receive free samples (starter packs) from branded drug suppliers, including Otezla®. There have been numerous studies demonstrating the relationship between pharmaceutical sample availability and clinician's prescribing behaviors, such that many academic centers have banned the practice of providing free samples to limit the influence on prescribing practices of its clinicians and resident physicians. Gilmore Tr. 898: 2-900:21; DTX-477.1; DTX-478.1; DTX-479.1.

1242. Amgen has not alleged that the substantial success of apremilast is attributable to the titration schedule in the Otezla® label.

1243. Indeed, the titration schedule in the Otezla® label has no meaningful benefit compared to what was already known about titrating apremilast in the prior art. DTX-153.2,7; DTX-157:1-2, 5; Gilmore Tr. 838:7-8; 849:11-12; 861:7-12. In addition, dermatologists routinely extend Otezla's titration beyond the titration schedule in the Otezla® label. Gilmore Tr. 877:3-4; 13-18.

1244. Many physicians have found that the titration schedule in the Otezla® label does not adequately alleviate the well-known gastrointestinal side effects associated with Otezla®. *See*, *e.g.*, JTX-98; JTX-99; JTX-100.

1245. It is the standard practice of many physicians to extend the titration of Otezla® so that the patient does not receive a total of 60 mg (30 mg bid) of apremilast until after 28 days of treatment. Gilmore Tr. 911;16-912:5. More specifically, when many physicians prescribe Otezla®, they provide with two, 14-day starter packs, and will instruct their patients to take 10mg a day for four days, 20 mg a day for four days, and 30 mg a day for the remainder of the 28 days. Gilmore Tr. 911:3-20. Afterwards, to the extent the patient wants to continue taking Otezla® they will fill the prescription and start taking 30 mg bid (twice daily). Gilmore Tr. 911:16-912:3.

1246. Celgene's advisory Board Summary shows that on numerous occasions Celgene received information from the "Key Opinion Leaders" on Celgene's own Advisory Boards explaining how they routinely depart from titration schedule in the Otezla® label. JTX-98; JTX-99; JTX-100.

1247. For example, under the heading "Fall Clinical Dermatology Advisory Board - For Lauderdale, FL March 28, 2015," the Celgene Advisory Board Summary reports as follows: "Many advisors adjust the dose of Otezla to alleviate tolerability issues. Use of 2 titration packs concurrently in order to more gradually increase dosage can reduce tolerability issues. Due to the number of gastrointestinal AEs [adverse events] observed, a doctor in one advisor's practice has been prescribing up to 3 titration packs to patients." JTX-98.4; Alexis Tr. 1860:3-25.

1248. As another example, under the heading "Maui Derm Advisory Board - Maui, HI, March 22, 2017," the Celgene Advisory Board Summary includes the following: "Advisors

discussed GI tolerability related to titration, with some noting that they use more than one starter pack. One advisor commented that they use several starter packs and may not even reach the BID dose if patients are achieving skin clearance (which some are) on the QD dose with no tolerability issues." JTX-98.11; Alexis Tr. 1861:2-13.

1249. Finally, a December 2017 email from Kimberly Wolf of Celgene containing a slide deck regarding feedback on Otezla®'s titration schedule reveals that GI tolerability is a major clinical barrier to starting and keeping patients on Otezla® and can often lead to discontinuation. JTX-99.1; JTX-100.25; Alexis Tr. 1862: 23-1864:9. The document also reports that to improve compliance, many physicians extend the titration schedule in the starter pack. JTX-99.1; JTX-100.25. Key Opinion Leaders' feedback revealed that physicians are often providing patients with two titration packs and are suggesting that patients double the length of time to achieve the 30-milligram BID dose. JTX-100.26. They are also giving one titration pack and then suggesting that patients titrate up to 30 milligrams once a day for a length of time before moving to 30 milligrams twice a day. *Id*

H. Apremilast Does Not Demonstrate Commercial Success.

1. Economic Disincentives Resulting From The '358 Patent.

1250. From an economic perspective, the performance of Otezla® fails to provide objective indicia of nonobviousness of the asserted claims of the '638 and '536 patents. Hofmann Tr. 1010: 6-12.

1251. This is in part because the '358 patent is a blocking patent to these claims and would disincentivize others from developing or commercializing a product that would practice them. Hofmann Tr. 1010:13-20, 1011:11-23, 1012:21-1013:12, 1019:22-1020:4.

1252. The '358 patent issued February 1, 2000, was assigned to Celgene and expired on October 30, 2018. DTX-174.1; Hofmann Tr. 1013:21-22, 1014: 6-8.

1253. Prior to its expiration, the ’358 patent was listed in the Orange Book for Otezla®. Hofmann Tr. 1012: 14-20; Vellturo Tr. 392:9-13; DTX-384.1000.

1254. The ’358 patent covers the compound apremilast in addition to the method of treating psoriasis, the oral dosage form, the PDE4 inhibitor and the dosing schedule. Hofmann Tr. 1012: 4-13; *see also* Alexis Tr. 311:2-17; Vellturo Tr. 381:22-383:25.

1255. The issue date of the ’358 patent (February 1, 2000) predates the earliest priority date of the ’638 and ’536 patents (March 20, 2002). Hofmann Tr. 1013:18-22, 1014: 2-5.

1256. Companies would be disincentivized from pursuing the manufacture, marketing, and commercial use of a product containing apremilast because it would necessarily infringe the ’358 patent. Hofmann Tr. 1012:4-1013:12, 1013:18-22, 1014: 6-10; Vellturo Tr. 393:2-11.

a. Ampyra Factors

1257. The Ampyra factors further confirm the economic disincentives for others to develop the invention claimed in the asserted claims of the ’638 and ’538 patents due to the blocking nature of the ’358 patent. Hofmann Tr. 1014: 12-22, 1019:18-1020:4.

i. The Likelihood of Successful Challenge to the Blocking Patent

1258. The ’358 patent has not been the subject of any litigation or challenges to its validity which supports the presence of the blocking nature of the ’358 patent. Hofmann Tr. 1015: 5-14.

ii. Costs Associated with Pursuing the Project in an Environment With Blocking Patents, Risk of Losing the Invention Race & Other Investment Opportunities

1259. Industry participants in 2000 would have known that Celgene had the rights to the ’358 patent, which included the apremilast compound as well as its use as a PDE4 inhibitor to treat psoriasis and psoriatic arthritis. Hofmann Tr. 1015:15-1016:8, 1016:13-1017:9.

1260. Parties would be disincentivized from incurring the costs to develop the technology of the ’638 and ’536 patents because of the significant risk that they would not be able to subsequently commercialize a product that practices those patents until at least October 2018 when the ’358 patent expires. Hofmann Tr. 1015:15-1016:8, 1016:23-1017:3.

1261. Companies would also infer that they would lag Celgene’s efforts in development of apremilast to treat psoriasis and psoriatic arthritis. Hofmann Tr. 1017:4-9.

1262. A company considering developing a product like Otezla would likely also be looking at other drug investment opportunities. Hofmann Tr. 1019:5-11.

1263. Given the costs associated with bringing a product like Otezla to market, a company would likely pursue other investment opportunities instead. Hofmann Tr. 1019:12-17.

iii. **Licensing**

1264. Celgene was looking for a potential co-development partner. Hofmann Tr. 1017:17-21.

1265. A license agreement grants the licensee rights to the licensor’s intellectual property in exchange for financial consideration and these agreements often occur between a university or research institution that has no intention or ability to commercialize on their own. Hofmann Tr. 1017:22-1018:13.

1266. Celgene, on the other hand, was not seeking to turn over rights to a compound because of the lack of capacity, experience, or resources to develop, sell, and commercially market a pharmaceutical product. Hofmann Tr. 1018:10-13.

1267. In fact, Celgene ultimately manufactured, marketed, and commercialized Otezla® on their own. Hofmann Tr. 1018:22-24.

1268. Because Celgene controlled the rights to the apremilast compound, to the extent others were interested in a co-development arrangement for apremilast, pursuit of such an

opportunity would be at the discretion of Celgene, and more costly for the other party. Hofmann Tr. 1018:11-13, 1017:22-24, 1060: 4-8.

1269. Amgen offers no evidence of financial term sheets or commercial negotiations to refute that during negotiations the potential development partners found the structure of the partnership and specific deal terms to be unfavorable and unacceptable, influencing their decision not to move forward. Hofmann Tr. 1018 at 18-22, 1062:6-7.

2. The Marketplace Performance of Otezla Does Not Provide Secondary Considerations of Nonobviousness.

1270. The marketplace performance of Otezla® is explained by factors unrelated to the claimed and allegedly novel features of the ’638 and ’536 patents. Hofmann Tr. 1010:23-1011:4, 1029:7-14. First, features that are responsible for Otezla’s marketplace performance were known in the prior art. Second, extrinsic factors beyond the patents at issue, such as marketing promotions and financial incentives, explain the marketplace performance of Otezla. Hofmann Tr. 1010:23-1011:4.

1271. As a result, there is no nexus between the marketplace performance of Otezla and the ’638 and ’536 patents. Hofmann Tr. 1020:11-20, 1029: 7-14.

a. The Marketplace Performance of Otezla® is Driven by Features that Were Known in the Prior Art.

1272. The alleged benefits of the apremilast compound that Amgen asserts purportedly drive the marketplace performance of Otezla® (its PDE4 inhibiting mechanism of action, the safety and efficacy, and the oral form) are all attributable to the apremilast compound disclosed in the ’358 patent and not to what is allegedly new in the claims of the ’638 and ’536 patents. Hofmann Tr. 1029:17-1030:7; *see also* Alexis Tr. 311:2-17; Vellturo Tr. 381:20-383:25, 386:12-387:6, 388:5-11, 388:16-389:2.

1273. As a result, these features fail to provide a nexus between the claimed marketplace performance of Otezla and the asserted claims of the '638 and '536 patents. Hofmann Tr. 1029:7-14.

1274. Yet, Dr. Vellturo admits that he did not consider the nexus between the marketplace success and the '358 patent. Vellturo Tr. 390:3-7.

1275. Moreover, Amgen fails to attribute any value to the eleven additional patents Celgene and Amgen list in the Orange Book as covering the manufacture and use of Otezla®. Hofmann Tr. 1030:11-16, 1030:20-1031:6; Vellturo Tr. 377:7-12; DTX-384.1000.

b. Marketing and Promotion of Otezla is a Driver of the Marketplace Performance of Otezla.

1276. In 2019 Celgene and Amgen spent $366 million on marketing and promotion for Otezla®. Hofmann Tr. 1033:1-4; JTX-82.63.

1277. To promote Otezla®, Celgene and Amgen execute various marketing efforts including direct-to-consumer advertising, sales representatives detailing to physicians, and the provision of product samples to patients. JTX-82.63.

1278. Amgen fails to address how these factors drive the marketplace performance of Otezla® in ways that are unrelated to the asserted claims of the '638 or '536 patents.

i. Direct-to-Consumer ("DTC") Advertising

1279. An internal Celgene strategy document indicates that "Direct to Patient Marketing" for Otezla® comprised approximately $168 million of the marketing budget in 2019. JTX-82.63. This document acknowledges that direct-to-consumer advertising is effective in generating patient interest and requests. Hofmann Tr. 1031:20-1032:2, 1032:7-12; JTX-82.84, 84. For example, patients who recall Otezla® consumer advertising are two times more likely to

start on the brand and health care providers receive more patient requests for Otezla than any other branded and promoted drug. Hofmann Tr. 1032:17-20; JTX-212.47.

1280. Celgene and Amgen spent $118 million on direct-to-consumer television advertising in 2019, about one-third of the total spend, on marketing and promotion. Hofmann Tr. 1032: 23-1033:4; JTX-82.83.

1281. Celgene has received a positive return on investment of 2:1 from its DTC TV ads. JTX-82.83.

1282. This evidence contradicts Dr. Alexis's testimony that patients only mention Otezla® TV ads after he offers Otezla® as a treatment option. *See* Alexis Tr. 312:5-16; Hofmann Tr. 1031:12-1032:2; 1032:5-20.

1283. In December 2016, Celgene received an Untitled letter from FDA's Office of Prescription Drug Promotion ("OPDP") regarding a DTC TV ad. DTX-401; Hoffman Tr. 1033:17-1034:7. The letter describes scenes from the commercial and states that the ad "misleadingly minimizes the risks associated with the use of Otezla," which "is especially problematic from a public health perspective given the serious risks associated with the drug." DTX-401.2-3; Hoffman Tr. 1034:11-1036:1.

1284. Dr. Vellturo did not account for the impact of this kind of DTC television advertising. Instead, his sole example of Amgen's DTC efforts was a single page from the Otezla® website listing in simple text the four drivers of marketplace performance he discusses. Hofmann Tr. 1033:5-18; Vellturo Tr. 364:11-20.

ii. **Detailing to Physicians and Speaker Programs**

1285. In addition to DTC advertising, Celgene and Amgen also use physician detailing to promote Otezla®. Hofmann Tr. 1036:22-1037:1.

1286. The performance of Celgene's sales representatives has been described as "Consistently Above Industry Average." Hofmann Tr. 1036:22-1037:1; JTX-214.9.

1287. Celgene also spends millions of dollars each year on speaker programs and receives a 2:06:1 ROI. JTX-217.1.

1288. Dr. Vellturo did not analyze the amount of money spent on physician detailing or speaker programs when conducing his analysis of share of voice. Vellturo Tr. 399:16-25.

iii. **Samples to Patients**

1289. Celgene and Amgen also provide Otezla® samples to health care providers to give to patients to whom they prescribe Otezla®. Hofmann Tr. 1037:3-10

1290. Otezla® samples were provided to 94 percent of patients prescribed Otezla® by dermatologists. Hofmann Tr. 1037:3-10; JTX-194.30.

1291. Dr. Vellturo did not consider the amount of money spent on product sampling in his analysis of Otezla®'s share of voice. Vellturo Tr. 400:5-7.

iv. **Discounts, [redacted] and Other Financial Incentives**

1292. Celgene and Amgen have offered pricing incentives to drive the marketplace performance of Otezla®. Hofmann Tr. 1037:11-1038:10.

1293. For example, Celgene and Amgen offer the Otezla® SupportPlus program, which provides a $0 co-pay program and the Otezla® bridge program, whereby patients may receive Otezla for up to three years at no cost. Hofmann Tr. 1037:11-1038:10; JTX-188.5; JTX-82.89; JTX-196.49. This makes Otezla® less expensive than even the generic options. Hofmann Tr. 1038:7-10.

1294. Internal Celgene documents reveal these programs are successful. *See, e.g.*, JTX-188.5; JTX-82.89; JTX-196.49.

[redacted]

VII. The Asserted Claims Of The '101 Patent Are Invalid.

A. The Person Of Ordinary Skill In The Art For The '101 Patent.

1400. As of March 27, 2008, a Person of Ordinary Skill in the Art ("POSA") related to the '101 patent would have been a scientist with a Ph.D. in a field such as organic or medicinal chemistry, solid-state chemistry, pharmaceutics, pharmacology, or a similar field, with one or two years of experience, or a scientist with a master's degree in these or similar fields, with an additional three or more years of experience, in research, development, and characterization of pharmaceutical compounds, including chiral synthesis and resolution of stereomeric compounds, analytical methods, such as x-ray crystallography for characterizing solid compounds. Gribble Tr. 587:13-24; Steed Tr. 1070:19-22, 1071:10-16.

1401. A POSA would have had a similar set of skills, experiences, and knowledge as of March 20, 2002. Steed Tr. 1071:17-20.

1402. Amgen has not offered a POSA definition that is materially different. Myerson Tr. 437:13-21; Steed Tr. 1071:21-25.

B. The Priority Date For The '101 Patent Is March 27, 2008.

1403. Claim 1 of the '101 patent is directed to the crystalline Form B of enantiomerically pure apremilast, comprising four XRPD peaks at about 10.1, 13.5, 20.7, and 26.9 degrees 2θ. *See* SOF ¶ 50; JTX-5.67; Steed Tr. 1069:14-22. Claim 15 is directed to a solid pharmaceutical composition comprising the crystalline Form B of enantiomerically pure apremilast recited in claim 1. *See* SOF ¶ 51; JTX-5.67; Steed Tr. 1069: 23-1070:1.

1404. It is undisputed that for the first time on March 27, 2008, new information was added to the '101 patent describing solid forms of apremilast, and methods for preparing and characterizing solid forms of apremilast. JTX-5.5-32 (newly added figures 1-28 disclosing results from analytical testing of apremilast crystalline forms A, B, C, D, E, F, and G, using four different solid form characterization techniques XRPD, DSC, TGA, and DVS); *see also* Steed Tr. 1082:4-24, 1077:15-1079:14; JTX-5.42-44 (10:39-13:5) (newly added definitions of terms and phrases associated with solid forms, crystalline and amorphous forms, and techniques for characterizing crystalline and amorphous forms); *see also* Steed Tr. 1084:1-14; JTX-5.46-51 (17:10-27:50) (newly added information to the "Detailed Description of the Invention" section of the '101 patent identifying seven apremilast crystalline forms A, B, C, D, E, F, and G, and methods for preparing and characterizing these solid forms of apremilast); *see also* Steed Tr. 1084:19-1085:11; JTX-5.62-66 (50:49-57:40) (newly added Example 12 describing apremilast solid form screening experiments that led to the identification of apremilast solid forms, including seven apremilast crystalline forms A, B, C, D, E, F, and G, and an amorphous form, methods for characterizing these solid forms of apremilast, and results from various studies performed on these apremilast solid forms); *see also* Steed Tr. 1088:11-1090:7.

1405. In particular, on March 27, 2008, Celgene added new information and data to the '101 patent describing the preparation, identification, and characterization of the claimed apremilast crystalline Form B for the first time. JTX-5.9-12 (newly added figures 5-8 disclosing results from analytical testing of apremilast crystalline Form B, using four different solid form characterization techniques XRPD, DSC, TGA, and DVS); *see also* Steed Tr. 1082:18-24, 1077:15-1079:14; JTX-5.42-44 (10:39-13:5) (newly added definitions of terms and phrases associated with solid forms, crystalline and amorphous forms, and techniques for characterizing crystalline and amorphous forms); *see also* Steed Tr. 1084:1-14; JTX-5.47-48 (19:60-21:22) (newly added information to the "Detailed Description of the Invention" section of the '101 patent identifying apremilast crystalline Form B, and methods for preparing and characterizing Form B); *see also* Steed Tr. 1086:19-1087:14; JTX-5.62-66 (50:49-57:40) (newly added Example 12 describing apremilast solid form screening experiments that led to the identification of apremilast solid forms, including seven apremilast crystalline forms A, B, C, D, E, F, and G, and an amorphous form, methods for characterizing these solid forms of apremilast, and results from various studies performed on these apremilast solid forms); *see also* Steed Tr. 1088:11-1090:7.

1406. A POSA would understand that to identify a specific crystalline form and distinguish it from other forms, a POSA would need to look at the characterization data (such as XRPD, DSC, TGA, and DVS) obtained from a polymorph screen "in total" to understand which solid forms "were pure forms and which forms were mixtures," to determine solid forms with "unique sets of data," at which point "they would give them a label, something like Form A or Form B." Steed Tr. 1079:3-11. For example, the data described in Figures 1-4 of the '101 patent

identify Form A, which would be different in many respects from the data described in Figures 5-8 corresponding to Form B. Steed Tr. 1079:12-14.

1407. Celgene sought and obtained claims to apremilast crystalline Form B only after adding the above-described new information to the '101 patent on March 27, 2008. Steed Tr. 1090:8-14. Indeed, when filing claims directed to apremilast crystalline Form B, Celgene cited the newly added sections to the '101 patent on March 27, 2008, as support. *See* JTX-18.282 (adding pending claims 47, and 50-63, among others, which later issued as claims 1-15 in the '101 patent, and citing as support "the figures and claims as filed" on March 27, 2008, more specifically citing "Figures 5-8" and "paragraphs [0121]-[0127]" of the '101 patent specification filed on March 27, 2008); *compare* JTX-18.31-33 (¶¶ [0121]-[0127]) *with* JTX-5.47-48 (19:60-21:22) (newly added information to the "Detailed Description of the Invention" section of the '101 patent identifying apremilast crystalline Form B, and methods for preparing and characterizing Form B). Thus, the named inventors of the '101 patent filed a new CIP application, with newly added information, after they prepared and characterized apremilast crystalline Form B. *Cf.* Gribble Tr. 631:7-10 (counsel for Amgen stating, "after the inventors prepared apremilast, they filed a new patent application, the 6 - - which ultimately issued as the '638 patent.").

1408. Further, the apremilast crystalline Form B and the XRPD peaks recited in claims 1 and 15 of the '101 patent are not redundant of the "enantiomerically pure apremilast" limitation and were central to the patentability and utility of the alleged invention claimed in the '101 patent. In particular, the '101 patent itself provides that apremilast may be found in seven different crystalline forms and one amorphous form. *See* JTX-5.63 (52:57:60); *see also* Steed Tr. 1088:25-1089:12. Further, during the prosecution of the '101 patent, Celgene successfully

distinguished the alleged invention claimed in the '101 patent from the '358 patent prior art by relying on the apremilast crystalline Form B and the XRPD peaks recited in claims 1 and 15 of the '101 patent. *See* JTX-18.329-41 (Celgene's Amendment and Response); *see id* at JTX-18.335-36 (Celgene arguing the '358 patent by Muller *et al.* did not anticipate the pending claims, including those later issued as claims 1 and 15, because the '358 patent "does not disclose the enantiomerically pure *crystal form* of the compound of formular (I) as recited in [pending] claim 47 [later issued as claim 1]," i.e., the apremilast crystalline Form B, and the '358 patent "is also silent as the XRPD data recited in the clam."); *see id* at JTX-18.393 (the Examiner explaining "Reasons for Allowance" as including "Muller et al. '358 [patent] does not disclose the instant X-ray pow[d]er diffraction pattern data of the instant compound, therefore it is distinct from the instant invention. The rejection of [the pending] claims 47 and 50-63 under 35 U.S.C. 102(b) [over] Muller et al. '358 [patent], or under 103(a) over Muller et al. '358 [patent] in view of Brittains' publication has been overcome").

1409. The appropriate priority date for claims 1 and 15 of the '101 patent is March 27, 2008, when the named inventors added data that would allow a POSA to recognize the inventors were in possession of the claimed apremilast crystalline Form B, along with other apremilast crystalline forms. Steed Tr. 1090:18-1091:11.

1410. Asserted claims 1 and 15 are not entitled to a priority date earlier than March 27, 2008, because the earlier related applications, including U.S. Provisional Application No. 60/366,515 ("the '515 application") that was filed on March 20, 2002, did not include any description, information, or data that would allow a POSA to conclude the named inventors were in possession of crystalline apremilast Form B claimed in claims 1 and 15 of the '101 patent. Steed Tr. 1109:23-1110:8.

1411. It is undisputed that the '515 application does not explicitly describe the claimed apremilast crystalline Form B, nor does it explicitly disclose any information from which a POSA could understand the named inventors were in possession of the claimed apremilast crystalline Form B as of March 20, 2002. JTX-43; Steed Tr. 1093:12-1094:1, 1110:9-11 ("Example 2 of that '515 application does not explicitly disclose a crystalline solid of apremilast. All we know is that it's a solid."); Myerson Tr. 1576:4-7 ("all experts agree that a POSA would have understood on March 20th, 2002, that Example 2 results in *some solid* form of apremilast") (emphasis added).

1412. Celgene filed the '515 application on March 20, 2002. JTX-43.2; Steed Tr. 1092:20-24. The '515 application lists Peter Schafer, George Muller, Hon-Wah Man, and Chuansheng Ge as the named inventors. JTX-43.2. Thus, Jean Xu who is a named inventor on the '101 patent is not listed as a named inventor on the '515 application. *Compare* JTX-5.2 *and* SOF ¶ 44 *with* JTX-43.2. Ms. Xu started working at Celgene on April 12, 2002, after the '515 application was filed. Xu Tr. 536:11-16. Ms. Xu performed the polymorph screen on apremilast identifying and characterizing the seven apremilast crystalline forms described in the '101 patent. Xu Tr. 535:21-536:10. Ms. Xu was asked to perform the apremilast polymorph screen in August 2003. Xu Tr. 540:5-19.

1413. A POSA would understand that the '515 application was directed to preparation and methods of using enantiomerically pure apremilast, Steed Tr. 1113:6-15, unlike the '101 patent which is directed to the solid forms of apremilast. Steed Tr. 1069:4-7. For example, the title of the '515 application is "Methods of Using and Compositions Comprising an Enantiomer of 2-[1-(3-Ethoxy-4-methoxypheny1)-2-methylsulfonylethy1]-4-acetylaminoisoindoline-1,3-dione," which includes the (+) enantiomer of the named molecule, i.e., apremilast. JTX-43.2.

The ’515 application’s title, unlike the ’101 patent title, does not refer to any solid form of apremilast. Steed Tr. 1081:23. As Amgen’s expert, Dr. Myerson, admitted, crystallization and polymorphism are not related to enantiomers. Myerson Tr. 435:19-22 (“Q. Do the concepts of crystallization and polymorphism that you’ve just discussed here have anything to do with racemates and enantiomers and stereoisomers? A. No.”)

1414. As another example, the ’515 application describes the field of invention as “methods of using and compositions comprising an enantiomer of 2-[1-(3-Ethoxy-4-methoxypheny1)-2-methylsulfonylethy1]-4-acetylaminoisoindoline-1,3-dione.” JTX-43.3; Steed Tr. 1093:3-11. Thus, from the description of the field of invention in the ’515 application, a POSA would understand that “[t]he ’515 application is directed to the single enantiomer of apremilast, not its solid forms.” Steed Tr. 1083:11-15.

1415. The’515 application contains only one figure, and it is related to the in vivo efficacy of apremilast in conscious ferrets, which does not disclose any information about any solid form of apremilast. JTX-43.7, 49. The ’515 application does not disclose any of the figures 1-28 that characterize and identify the seven solid forms, including Form B, of apremilast described in the ’101 patent. Steed Tr. 1093:12-15.

1416. The ’515 application includes 11 examples. JTX-43.27-42. The ’515 application does not disclose any examples regarding solid forms screening of apremilast like Example 12 disclosed in the ’101 patent. Steed Tr. 1093:16-19. The ’515 application does not include any information about performing a solid form screening of apremilast or any solid form characterization data. Steed Tr. 1093:20-1094:18.

1417. According to Amgen, the priority date of the asserted claims of the ’101 patent is March 20, 2002. In support of this priority claim, Dr. Myerson points to the ’515 application and

says that it inherently discloses the claimed apremilast crystalline Form B. Myerson Tr. 1576:8-9. The only disclosure in the '515 application that Dr. Myerson points to as purportedly inherently disclosing the claimed apremilast crystalline Form B is a half-sentence in Example 2 of the '515 application that states that an enantiomerically pure apremilast "residue [was] recrystallized from a binary solvent containing ethanol (150 mL) and acetone (75 mL)." JTX-43.29 (ll. 29-30); Myerson Tr. 1576:10-1577:1. A POSA, however, would not readily and unambiguously learn from reading this half-sentence that the named inventors were in possession of the claimed invention with all of its limitations, including apremilast crystalline Form B having an XRPD comprising peaks at about 10.1, 13.5, 20.7, and 26.9 degrees 2θ. JTX-5.67 (claim 1); Steed Tr. 1091:25-1092:12.

1418. It is undisputed that Example 2 is a recipe for the chemical synthesis and purification of enantiomerically pure apremilast. JTX-43.28-30; Steed Tr. 1095:4-15, 1095:21-1097:11; Sacchetti Tr. 1172:5-17; Myerson Tr. 1576:15-1577:1. Dr. Myerson has further admitted that the concepts of crystallization and polymorphism are not related to enantiomers. Myerson Tr. 435:19-22 ("Q. Do the concepts of crystallization and polymorphism that you've just discussed here have anything to do with racemates and enantiomers and stereoisomers? A. No.").

1419. The Example 2 recipe for the chemical synthesis and purification of enantiomerically pure apremilast includes four steps. JTX-43.28-29; Steed Tr. 1095:21-1097:11. A POSA would only understand that by following this recipe, a solid sample of apremilast could be prepared. Steed Tr. 1095:4-20. It is undisputed that a solid compound may exist in different solid forms, including crystalline and amorphous solids. Steed Tr. 1072:22-1073:3. The apremilast solid obtained at the end of Example 2 "could be present as an amorphous or a

crystalline solid," and a POSA would not "necessarily know because there is no analysis reported," "they would not actually know whether they got any particular crystalline form or a mixture or -- or amorphous form." Steed Tr. 1101:15-1102:4. The '101 patent itself provides that apremilast may be found in seven different crystalline forms and one amorphous form. *See* JTX-5.63 (52:57:60); *see also* Steed Tr. 1088:25-1089:12.

1420. It is undisputed that a POSA reading the half-sentence Amgen relies on would understand it to describe a purification step at the end of the chemical synthesis of apremilast to remove impurities left behind from the final chemical reaction in the path to synthesizing enantiomerically pure apremilast. JTX-43.29 (ll. 29-30); Steed Tr. 1097:21-24. A POSA would understand the goal of this purification step is to "go from a crude material" called the "residue" in Example 2 to "a purified solid" with fewer impurities than the "residue." Steed Tr. 1098:21-1099:5; *see also* Sacchetti Tr. at 1185:14-16 (explaining that a POSA would expect the result of this recrystallization procedure to be "chemically pure apremilast").

1421. It is undisputed that Example 2 describes the product obtained at the end of the fourth step of apremilast synthesis as a "solid" without any additional description. JTX-43.29 (l. 30). Tellingly, the solid obtained in step 2 of apremilast synthesis is described as a "crystalline solid." JTX-43.28 (l. 29) (emphasis added). A POSA would understand from the Example 2 disclosure that the named inventors obtained a solid at the end of step 2 that, based on visual investigation, appeared to be crystalline and the inventors explicitly noted that observation in step 2 of Example 2. Steed Tr. 1102:6-23. In contrast, a POSA would understand from the Example 2 disclosure that the named inventors of the '515 application did not visually observe the solid obtained in step 4 to be a crystalline solid. Steed Tr. 1102:24-1103:11. Nor did the

named inventors of the '515 application provide any data in Example 2 to further characterize and describe the solid obtained in step 4. Steed Tr. 1103:18-1104:21; Myerson Tr. 1624:19-22.

1422. Relatedly, Ms. Xu, a named inventor listed on the '101 patent but who is not listed as an inventor on the '515 application, prepared the apremilast polymorph screening report dated April 2, 2004, which describes the identification and characterization of seven apremilast crystalline forms. JTX-126.3; Xu Tr. 541:5-16. In this report, Ms. Xu describes apremilast crystalline Forms A and B both as appearing as "a white, flaky crystalline solid." JTX-126.2, 12, 13 (emphasis added). Thus, when Ms. Xu prepared an apremilast crystalline form, she knew how to visually describe it as such. Notably, such characterization is completely absent from the step 4 disclosure of Example 2 that Dr. Myerson relies on. *Cf*. JTX-43.29 (l. 30).

1423. A POSA reading Example 2 would understand that the named inventors were not interested in describing, identifying, or characterizing the solid form of the "solid" obtained at the end of Example 2—rather, they were interested in preparing an enantiomerically pure apremilast to test and characterize in solution-based assays described in other Examples in the '515 application. Steed Tr. 1101:15-1102:4 ("in fact, there is no analysis of that solid, and a person of skill wouldn't care what the solid form was because their purpose is to purify the apremilast. They don't really care what solid form it's in. So, it could be present as an amorphous or a crystalline solid, and a POSA wouldn't – wouldn't even necessarily know because there's no analysis reported, and that's not the purpose of the exercise."), 1103:24-1104:21; *see also* JTX-5.63 (52:57:60) (the '101 patent itself providing that apremilast may be found in seven different crystalline forms and one amorphous form); *see also* Steed Tr. 1088:25-1089:12 (testifying about JTX-5.63 (52:57:60)).

1424. It is undisputed that Example 2 discloses data solely related to the chemical purity of the "solid" obtained at the end of the last step of Example 2. JTX-43.29-30 (disclosing the enantiomeric purity of the obtained solid as 98% ee, also disclosing data from chiral HPLC, showing the solid contained 98.7% S-isomer and 1.2% R-isomer, and proton and carbon 13 NMR data); *see also* Steed Tr. 1103:14-1104:21 (explaining chiral HPLC is a "solution technique that would tell a person of skill whether they've been successful in making apremilast as one enantiomer or not," and that proton and carbon 13 NMR is also a "solution technique," and "another measure of purity.").

1425. It is undisputed that Example 2 does not disclose any data related to the solid form of the "solid" obtained at the end of last step that could inform a POSA whether the solid is crystalline, amorphous, or a mixture. JTX-43.29-30; Steed Tr. 1101:15-1102:4 (the solid "could be present as an amorphous or a crystalline solid," and a POSA would not "necessarily know because there is no analysis reported," "they would not actually know whether they got any particular crystalline form or a mixture or -- or amorphous form."); Myerson Tr. 120:1-4.

1426. As Dr. Myerson testified, "you can only know [a crystalline form] exists after you've discovered it and characterized it." Myerson Tr. 1632:6-12. Further, a POSA understands that a polymorph is identified by its unique set of characterization data. Steed Tr. 1079:3-14. Because Example 2 does not include any descriptive or analytical data regarding the solid form of the "solid" obtained at the step 4, Example 2 does not show that the named inventors of the '515 application were in possession of a crystalline solid form of apremilast, let alone Form B.

1427. The half-sentence in Example 2 leaves out many details about how the named inventors performed the recrystallization step. JTX-43.29 (ll. 29-30); Steed Tr. 1100:23-1101:14

(no information provided regarding the amount of "the residue," no information regarding the order of addition of the two solvents, no information regarding how to dissolve the residue in the solvents, and no information on how to precipitate apremilast from the obtained solution).

1428. A POSA would understand that depending on the undisclosed details of the recrystallization step, the named inventors could have obtained Form A from the mixture of acetone and ethanol used in Example 2, if fast crystallization was used, or Form B, if slow crystallization was used, any other crystalline, or an amorphous form, depending on how the recrystallization step was performed. Steed Tr. 1105:10-22 ("the solid form, crystalline mixture, whichever crystalline form it might be, or even amorphous, would depend upon how the person of skill chose to do the recrystallization step. And so -- and so depending upon how they did it, we've already seen that Form A can result from ethanol and acetone if fast crystallization is used, Form B from slow, and any one of the other crystalline forms could also result depending upon how the crystal- -- how the recrystallization step is done."), 1134:23-1135:4. And if the named inventors had obtained a mixture, then the properties of the obtained mixture would be a combination of each component's properties. Steed Tr. 1136:24-1137:3, 1137:20-1138:2, 1139:22-1140:6.

1429. Amgen's expert, Dr. Myerson, only offered a conclusory statement that "the inventors were in possession of a crystalline form of apremilast that they could then identify via XRPD." Myerson Tr. 1577:2-6. Dr. Myerson did not cite any disclosure in Example 2, in the '515 application, or even outside the four corners of the '515 application to support this assertion. Id. As Dr. Myerson admitted, there is none. Myerson Tr. 1623:21-1624:22, 1625:14-1626:2 (testifying that "I don't have any data that would demonstrate what form [Celgene] made," he hasn't "seen any lab notebooks" to determine what form Celgene made, and has seen

no analytical data for the product of Example 2 in the '515 application); *see also* JTX-43.29-30; Steed Tr. 1101:15-1102:4 ("in fact, there is no analysis of that solid, and a person of skill wouldn't care what the solid form was because their purpose is to purify the apremilast. They don't really care what solid form it's in. So, it could be present as an amorphous or a crystalline solid, and a person wouldn't – wouldn't even necessarily know because there's no analysis reported, and that's not the purpose of the exercise."), 1105:10-22 ("the solid form, crystalline mixture, whichever crystalline form it might be, or even amorphous, would depend upon how the person of skill chose to do the recrystallization step. And so -- and so depending upon how they did it, we've already seen that Form A can result from ethanol and acetone if fast crystallization is used, Form B from slow, and any one of the other crystalline forms could also result depending upon how the crystal- -- how the recrystallization step is done.").

1430. Amgen has not presented any evidence that could show the named inventors of the '515 application had conceived of a crystalline form of apremilast by March 20, 2002, to be able to describe it in the '515 application. The only named inventors listed on the '515 application that the Court heard from were Dr. Peter Schafer and Dr. George Muller. Neither Dr. Schafer's testimony nor Dr. Muller's testimony did include any statement regarding apremilast solid forms. Schafer Tr. 128:24-186:3; Muller Tr. 518:11-524:9.

1431. After assuming without support that Example 2 describes a crystalline apremilast solid, as opposed to an amorphous form or a mixture, Amgen focuses on arguing that the crystalline solid obtained is inherently Form B. The evidence Amgen presented at trial, however, falls short. The only evidence Amgen offered at trial to support its asserted priority date of March 20, 2002, is data from 13 experiments submitted by three generic companies several years after the alleged priority date to the European Patent Office ("EPO") as part of an

opposition proceedings. Myerson Tr. 1577:25-1578:6. It is undisputed that none of the data that Dr. Myerson relies on was disclosed in the '515 application as of March 20, 2002. There is, however, a dispute between the experts whether these 13 experiments submitted by the three generic companies were proper replications of Example 2. *Compare* Myerson Tr. 1577:25-1578:6 *with* Sacchetti Tr. 1199:25-1200:10 *and* Steed Tr. 1156:25-1157:10.

1432. Even if following Example 2 under certain circumstances may lead to apremilast crystalline Form B, that does not show following Example 2 would always lead to apremilast crystalline Form B. Amgen's expert, Dr. Myerson, admitted that to demonstrate that a disclosure inherently results in an intended outcome, "an example has to always produce the patented, in this case the patented crystal form, every time without exception." Myerson Tr. 1593:22-1594:4. Dr. Myerson, however, did not offer any testimony or evidence that the experiments submitted by the three generic companies to the EPO cover every possible variation of the recrystallization step generally described in Example 2.

1433. The '101 patent explains that the recrystallization step of Example 2, under certain circumstances, would lead to apremilast crystalline Form A. In particular, the '101 patent states apremilast Form A "can be obtained from various solvents including but not limited to solvent systems comprising acetone, ethanol, and mixtures thereof," "using a fast cooling crystallization process." JTX-5.46 (18:40-45); Steed Tr. 1085:18-1086:17; Sacchetti Tr. 1172:24-1173:6. The method described in the '101 patent for preparing Form A falls within the general procedure described in Example 2 of the '515 application. Steed Tr. 1105:10-22; Myerson Tr. 1615:2-16.

1434. Similarly, Ms. Xu's apremilast polymorph screening report states that Form A "was recrystallized from acetone/ethanol after rapid cooling to 15°C for 105 min." JTX-126.7;

Xu Tr. 541:5-22. This again uses the same binary solvent system described in Example 2 of the '515 application that Dr. Myerson relies on. JTX-43.29 (ll. 29-30).

1435. Amgen's expert, Dr. Myerson, admitted that "the specific crystalline form that is produced using a combination of ethanol and acetone" "can be influenced by the cooling rate." Myerson Tr. 1597:3-10. Because Example 2 is silent on the cooling rate, all possible cooling rates would fall within the scope of Example 2. JTX-43.29 (ll. 29-30); Steed Tr. 1100:23-1101:14 (explaining various parameters that a POSA could vary to perform the recrystallization step of Example 2, including parameters related to the cooling). Thus, the recrystallization step described in Example 2 of the '515 application does not always lead to apremilast crystalline Form B.

1436. As another example, Celgene itself represented to the EPO that following Example 2 would lead to apremilast crystalline Form C, not Form B. JTX-225.14-15; Steed Tr. 1106:5-15; 1108:1-8 ("Celgene itself represented to the European Patent Office that following the teachings of Example 2 including that recrystallization step results in crystalline Form C, not -- not Form B. And Celgene is the patent proprietor, so they should know what they're doing."), 1108:13-1109:7 (explaining that Celgene submitted data from experiments that Celgene maintained replicated the Example 2 recrystallization step in three different ways, all of which led to Form C); *see also* Myerson Tr. 1620:1-6.

1437. These Celgene statements are summarized in the EPO decision dated June 23, 2017 (JTX-225.2,) before Celgene originally filed the instant suit against Defendants in 2018. SOF ¶ 99 ("Between June 26, 2018 and July 11, 2018, Celgene Corp. ("Celgene") filed suit against the Defendants alleging infringement of varying combinations of the '536 Patent, the '638 Patent, and the '101 Patent against each Defendant").

1438. Amgen's expert, Dr. Myerson, attempted to dismiss these Celgene's statements by testifying that "Celgene just made a mistake." Myerson Tr. 1587:5. This post hoc characterization is, however, contrary to what Celgene represented at the EPO. JTX-225.14 ("E22 is the experimental data supplied by [patent proprietor, i.e., Celgene] concerning the synthesis and recrystallization procedure of the Apremilast. The synthesis is identical to that [Example 2]."); JTX-225.15-16 (summarizing various arguments Celgene made to convince the EPO that the experiments it submitted replicated Example 2 while those submitted by the generics did not).

1439. The EPO sided with the generic companies and invalidated the European patent they challenged. JTX-225.17. The EPO's conclusion is not relevant at least because the EPO decision was based on a different legal standard regarding a different legal issue. JTX-225.10 (discussing the issue of novelty under Article 54 of the European Patent Code); JTX-225.12 (discussing two relevant European patent decisions regarding burden and standard of proof); Steed Tr. 1109:8-22 ("I'm not an expert in European law but my point here is that Celgene itself is stating to the European Patent Office that when they do Example 2, including that recrystallization step relied upon by Dr. Myerson, they get Form C, not Form B.")

1440. Based on the information provided in Example 2, including the general procedure described for the recrystallization step, and the disclosed chemical and enantiomeric purity data, a POSA would not immediately discern whether the obtained "solid" is "any particular crystalline form, or a mixture, or -- or amorphous form". Steed Tr. 1101:15-1102:4. In other words, a POSA would not understand that following Example 2 of the '515 application would inevitably or necessarily lead to apremilast crystalline Form B. Steed Tr. 1103:24-21, 1105:10-22.

1441. The testimony of the other polymorph expert in this case undermines Amgen's assertion that following Example 2 of the '515 application would inevitably and necessarily lead to apremilast crystalline Form B. In particular, Dr. Sacchetti testified that a POSA following Example 2 would obtain apremilast crystalline Form A. Sacchetti Tr. 1194:6-19.

1442. Example 2 of the '515 application does not inherently describe the claimed apremilast crystalline Form B because following Example 2 does not inevitably lead to Form B. Steed Tr. 1110:11-20 ("depending on how the person of skill chooses to carry out recrystallization, it could result in -- well, we don't know, anything. But certainly, we've looked to the possibility of it being Form A if it was crystallized quickly. There are ways to do it that give rise to Form B—the opponents in the European Patent litigation opposition showed that. And Celgene itself maintains that it forms Form C.")

1443. Therefore, the '515 application does not convey to a POSA that the named inventors were in possession of the claimed apremilast crystalline Form B, nor does it describe the claimed apremilast crystalline Form B either explicitly or inherently. Steed Tr. 1109:23-1110:20. Thus, the '515 application does not meet the written description requirements to support Amgen's asserted March 20, 2002, priority date. Instead, the proper priority date for the asserted claims of the '101 patent is March 27, 2008, when the disclosure that characterized Form B and other solid forms of apremilast was added to the patent specification. Steed Tr. 1090:18-1091:11.

C. Scope And Content Of The Prior Art As of March 27, 2008, For The '101 Patent.

1. Polymorphism

1444. A solid compound may exist in different solid forms, including crystalline and amorphous solids. Steed Tr. 1072:22-1073:3. An illustrative example is the compound silicone

dioxide, which exists in a crystalline solid form known as quartz in which the molecules form a specific regular repeating arrangement leading to quartz' faceted crystal look. Steed Tr. 1073:4-17. The same chemical compound silicone dioxide also exists in an amorphous solid form known as glass in which the silicon and oxygen atoms are bonded irregularly and randomly without any repeating order or pattern. Steed Tr. 1073:4-17. Because of their different solid form arrangements, quartz and glass have different properties. Steed Tr. 1073:16-17.

1445. A crystalline solid is a solid form in which the atoms and molecules are arranged in a regular repeating three-dimensional arrangement. Steed Tr. 1073:9-11; Myerson Tr. 425:17-426:4.

1446. Polymorphism occurs when a chemical compound can crystallize into more than one three-dimensional arrangement. Steed Tr. 1074:1-10; Myerson Tr. 426:19-427:23.

1447. By 2008, polymorphism was well-known and well-documented in pharmaceutical compounds. Steed Tr. 1074:14-17. As explained in a 1997 article by Harry Brittain published in the Journal of Pharmaceutical Sciences ("Brittain 1997"), "the occurrence of polymorphism is quite common for organic molecules, and a great number of polymorphic drug compounds have been noted and cataloged." SOF ¶ 137; DTX-98.1; Steed Tr. 1074:17-21. In fact, "around 57 percent of pharmaceuticals [] have more than one solid form." Steed Tr. 1074:22-24.

1448. It is undisputed that the specific crystalline form of an active pharmaceutical compound may impact its pharmaceutical properties, including bioavailability, manufacturability, and shelf life. Steed Tr. 1075:5-20; Myerson Tr. 428:9-23; Sacchetti Tr. 1169:20-23 ("pharmaceutical scientists had long before [1992] recognized that polymorphs can have different properties that affect their manufacturability, stability, and bioavailability."); *see also* DTX-128.12 ("Some new drug substances exist in different crystalline forms which differ in

their physical properties. [] Differences in these forms could, in some cases, affect the quality or performance of the new drug product.")

1449. By 2008, as explained in Brittain 1997, a POSA recognized that "[a] full evaluation of possible variations in crystallography that might be encountered is now essential for the development for a new drug compound because the Food and Drug Administration (FDA) requires that analytical procedures be used to detect polymorphic, hydrated, or amorphous forms of the drug substance." DTX-98.1; *see also* DTX-128.12; Steed Tr. 1075:24-1076:8 ("it was absolutely vital, as of that time frame and before," "to have a good understanding of what possible solid forms were out there, and then choose a solid form to formulate as a drug product that would give desirable and consistent properties."); Sacchetti Tr. 1169:24-1170:10 (FDA and other regulatory agencies require pharmaceutical companies to include a specific test that identifies the polymorphic form).

1450. It is undisputed that a POSA would have routinely performed a polymorph screen on a pharmaceutical compound of interest as part of the pre-formulation stage in a drug development program. Steed Tr. 1076:9-11; Sacchetti Tr. 1169:11-19 (as of 1992, "polymorph screening was a routine established experiment" in the pharmaceutical industry, which was done "for every new chemical entity that was going to be advanced into clinical trials"); Myerson Tr. 1630:3-8 (testifying that when "a compound goes into preclinical development at a pharmaceutical company, that generally involves a polymorph screen"); *see also* JTX-224.3-4 ("Systematic investigation of a compound to determine whether it is prone to polymorphism [] is routine practice in pharmaceutical pre-formulation studies. Identification of the different polymorphic forms of a drug substance determination of their chemical and physical properties, thermodynamic stabilities, and temperatures and rates of interconversion are essential for

ensuring drug preparations with reproducible behavior."); DTX-128.28 (in a decision tree, instructing a POSA to "Conduct polymorphism screen on drug substance."); Steed Tr. 1118:18-1119:3 (explaining the teachings of DTX-128.28).

1451. A polymorph screen typically includes a series of "experiments in which, very simply, the compound is crystallized under a variety of different conditions to see what solid forms [] it has. And, so these are very, very trivial experiments. They're as simple as just dissolving the compound in solution. It could even be water and letting it cool and crystalize and then analyzing the outcome." Steed Tr. 1077:1-9.

1452. By 2008, there were known methods for preparing and identifying polymorphs in a polymorph screen. For example, a chapter written by Guillory in the well-known book titled "Polymorphism in Pharmaceutical Solids," by Harry Brittain published in 1999 ("Guillory"), teaches polymorph screening methods. SOF ¶ 141; DTX-125.7; *see also* Steed Tr. 1120:5-11 (explaining the teachings of DTX-125.7). Guillory teaches a POSA "what solvents they should incorporate within their polymorph screen." Steed Tr. 1120:25-1121:11. In particular, Guillory teaches "[i]n determining what solvents to use for crystallization, one should be careful to select those likely to be encountered during formulation and processing." DTX-125.14; *see also* Sacchetti Tr. 1169:24-1170:11-20 (polymorphic screening typically include solvents that are commonly used in pharmaceutical processing); Myerson Tr. 1628:3-6. "And processing includes making the drug substance in the first place so the synthesis procedure like" those described in the '052 publication. Steed Tr. 1121:19-25.

1453. By 2008, there were several methods known in the art for characterizing different solid or crystalline forms prepared in a polymorph screen, including x-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and

dynamic vapor sorption (DVS), solubility, melting point, or other techniques. Steed Tr. 1077:15:1078:11.

1454. XRPD, for example, was commonly used in the pharmaceutical industry "to determine what crystalline form has been made and to verify that a crystalline form is being made reproducibly." Myerson Tr. 429:21-25; *see also* DTX-455.39 (due "to its inherent simplicity of performance, the technique of x-ray powder diffraction (XRPD) is the predominant tool [and] is eminently suited for the routine characterization of polymorphs"). The XRPD technique was known to generate "effectively, a fingerprint of a particular polymorph form as long as it's a pure form," thus it was known to generate "a different pattern of peaks for each isolated pure form." Steed Tr. 1078:18-22.

1455. A POSA would have used these analytical techniques to identify a polymorph and to distinguish it from other forms "by looking at the characterization data in total," to find out which forms obtained from a polymorph screen were pure and which ones were mixtures, and to determine unique forms obtained and label them with unique identifiers, such as Form A or Form B. Steed Tr. 1079:3-14.

2. Apremilast And The '052 Publication

1456. U.S. Patent Application Publication No. US 2003/0187052 A1 ("the '052 publication") published on October 2, 2003. SOF ¶ 153; DTX-179.1; Steed Tr. 1113:9-10. If the priority date is March 27, 2008, it is undisputed that '052 publication is prior art to the asserted claims of the '101 patent.

1457. The '052 publication is "what the '515 application eventually was published as." Steed Tr. 1113:6-8. The '052 publication generally describes a method for preparing enantiomerically pure apremilast, methods for using it, including preparing pharmaceutical compositions comprising enantiomerically pure apremilast. DTX-179.1 (Abstract), 15 (Example

2, preparation of compound A); Steed Tr. 1113:11-15; Sacchetti Tr. 1175:23-1176:5 ("the '052 publication, teaches how to make an enantiomerically pure apremilast. It does so in Example 2 which is a recrystallization from a solution of two parts ethanol, one part acetone.").

1458. The '052 publication teaches that after the chemical synthesis of apremilast, the crude apremilast residue was purified using a 2:1 mixture of ethanol and acetone as solvents. DTX-179.15 (¶ [0103]); Steed Tr. 1122:12-1123:7.

1459. The '052 publication discloses examples of preclinical testing performed on enantiomerically pure apremilast. DTX-179.15-19 (Examples 3-8); Myerson Tr. 1628:22-1629:18. These examples support apremilast's described utility in "treating and/or preventing diseases ameliorated by the reduction of TNF-α or the inhibition of PDE4." DTX-179.1 (Abstract).

1460. The '052 publication teaches incorporating enantiomerically pure apremilast into pharmaceutical compositions and single unit dosage forms as "useful in the treatment and prevention of a variety of diseases and disorders." DTX-179.7 (¶ [0032]); Steed Tr. 1113:18-1114:4; Sacchetti Tr. 1176:11-14 (the '052 publication teaches the utility of apremilast in treating certain diseases and disorders).

1461. The '052 publication discloses examples of solid oral pharmaceutical compositions comprising enantiomerically pure apremilast. DTX-179.19-20 (Examples 9-10); Sacchetti Tr. 1176:6-10. The '052 publication further discloses examples of single unit dosage forms of enantiomerically pure apremilast, including those containing crystalline or amorphous solids. DTX-179.11 (¶ [0062]); Steed Tr. 1114:8-16.

D. The Claims Of The '101 Patent Are Obvious As Of March 27, 2008.

1462. Claim 1 of the '101 patent is directed to the crystalline Form B of enantiomerically pure apremilast, comprising four XRPD peaks at about 10.1, 13.5, 20.7, and

26.9 degrees 2θ. *See* SOF ¶ 50; JTX-5.67; Steed Tr. 1069:14-22. Claim 15 is directed to a solid pharmaceutical composition comprising the crystalline Form B of enantiomerically pure apremilast recited in claim 1. *See* SOF ¶ 51; JTX-5.67; Steed Tr. 1069: 23-1070:1.

1463. At trial, Prof. Steed testified that claims 1 and 15 of the '101 patent would have been obvious in view of the '052 publication and the knowledge of a POSA. Steed Tr. 111:2-1113:2, 1125:10-12, 1127:12-17 (testifying about the legal standard applied); 1125:15-22. Additionally, Prof. Steed testified that claims 1 and 15 of the '101 patent would have been obvious in view of the '052 publication, Brittain 1997, the ICH Guidelines, Guillory, Brittain 1999, and the knowledge of a POSA. Steed Tr. 1125:23-1126:4.

1464. Amgen has not offered any evidence to rebut opinions offered by Prof. Steed, Defendants' expert, that the asserted claims of the '101 patent would have been obvious to a POSA in view of the prior art as of March 27, 2008. Steed Tr. 1111:15-24; Myerson Tr. 1613:5-17. Amgen did not cross examine Defendants' expert, Prof. Steed, on his opinions regarding the state of the art pertinent to the '101 patent as of March 27, 2008, including the teachings of the '052 publication. The only line of cross examination that Amgen could even argue is related to Prof. Steed's opinions on obviousness as of March 27, 2008, was directed to Prof. Steed's testimony in a different case, involving a different compound, different patent, and different prior art. *Compare* Steed Tr. 1149:2-1153:8 *with* Steed Tr. 1158:8-16. And, Amgen's own expert, Dr. Myerson did not offer any testimony at all on this issue. Myerson Tr. 1613:5-17.

1465. As explained in more detail below, each of the above prior art combinations would render the claimed crystalline apremilast Form B obvious to a POSA: they would have motivated a POSA to perform a polymorph screen on the known enantiomerically pure apremilast, which would have included known solvents used in the last step of apremilast

synthesis and purification, with a reasonable expectation of preparing crystalline apremilast Form B. Steed Tr. 1127:20-1128:10.

1466. Further, as explained below, the remaining elements of claims 1 and 15 would have been either inherent in the crystalline apremilast Form B prepared and identified in the polymorph screen (the XRPD peaks at about 10.1, 13.5, 20.7, and 26.9 degrees 2θ), or explicitly taught in the '052 publication ("solid pharmaceutical composition"). Steed Tr. 1128:10-13.

1. A POSA Would Have Been Motivated To Perform A Routine Polymorph Screen on The Known Enantiomerically Pure Apremilast Using Known Solvents Ethanol and Acetone.

1467. As discussed above in Section VII.C.2, the '052 publication teaches and motivates a POSA to prepare an oral pharmaceutical composition comprising enantiomerically pure apremilast for administration to a patient, including sterile solids (crystalline or amorphous). DTX-179.11 (¶ [0062]), 19-20 (Examples 9-10 disclosing examples of solid oral pharmaceutical compositions comprising enantiomerically pure apremilast); Steed Tr. 1114:8-16; *see also* DTX-179.1 (Abstract), 15 (Example 2, preparation of compound A); Steed Tr. 1113:11-15; Sacchetti Tr. 1175:23-1176:5 ("the '052 publication, teaches how to make an enantiomerically pure apremilast. It does so in Example 2 which is a recrystallization from a solution of two parts ethanol, one part acetone."); DTX-179.7 (¶ [0032]); Steed Tr. 1113:18-1114:4; Sacchetti Tr. 1176:11-14 (the '052 publication teaches the utility of apremilast in treating certain diseases and disorders); DTX-179.15-19 (Examples 3-8 disclosing examples of preclinical testing performed on enantiomerically pure apremilast); Myerson Tr. 1628:22-1629:18.

1468. These teachings would have motivated a POSA to perform a polymorph screen, which is a "routine task of pharmaceutical pre-formulation," by crystallizing apremilast under different sets of conditions to "see what crystalline or amorphous solids it actually forms. So, they could then select amongst them which would be the most appropriate to formulate into a

single unit dosage form." Steed Tr. 1114:17-1115:8. Amgen's expert, Dr. Myerson agrees. Myerson Tr. 1629:19-1630:13 (admitting that based on the teachings of the '052 publication, a POSA would have been "interested in finding a crystalline solid form that met a series of properties, one of which would be polymorphic stability," and to do so, a POSA would have undertaken a polymorph screen.); *see also* above Section VII.C.1 (¶¶ [248-250].)

1469. The '052 publication discloses a specific solvent system used in the last step for preparing enantiomerically pure apremilast: a 2:1 mixture of ethanol to acetone used for purifying the crude apremilast residue via recrystallization. DTX-179.15 (¶ [0103]). Amgen's expert, Dr. Myerson agrees. Myerson Tr. 1628:7-11.

1470. By 2008, a POSA would have understood that an obvious first step in a polymorph screen on apremilast is to perform a screen including ethanol and acetone as solvents. Steed Tr. 1126:14-18; Xu Tr. 538:24-540:4 (testifying that in planning a polymorph screen in the 1997 to 2002 timeframe, they would "know what is a recrystallization solvent [the process chemist] use[d]" and that they would use the solvent they used in the last step), 542:8-21 (testifying that she included ethanol in her polymorph screen as a solvent because that was a solvent used in the last step of apremilast synthesis).

1471. A POSA would have understood the teachings of the '052 publication regarding solvents as an important factor in "in determining polymorphic outcome." Steed Tr. 1122:25-1123:3. Therefore, in view of the '052 publication, a POSA would have been motivated to perform a polymorph screen on enantiomerically pure apremilast using ethanol and acetone as solvents.

1472. Other prior art references discussed above in Section VII.C.1 would have also motivated a POSA to perform a routine polymorph screen on the enantiomerically pure

apremilast including the solvent system used in the last step of apremilast synthesis disclosed in the '052 publication. Steed Tr. 1115:9-18; *see also* above Section VII.C.1 (¶¶ [247-250]).

1473. First, Brittain 1997 would have motivated a POSA to conduct a polymorph screen. Brittain 1997 teaches a POSA that "[a] full evaluation of possible variations in crystallography that might be encountered is now essential for the development for a new drug compound because the Food and Drug Administration (FDA) requires that analytical procedures be used to detect polymorphic, hydrated, or amorphous forms of the drug substance." DTX-98.1. Based on these teachings, Prof. Steed explained that a POSA "by the 2008 time frame was well-versed in the need to carryout polymorph screening in order to fulfill the requirements of the FDA." Steed Tr. 1115:22-1116:14.

1474. A POSA motivated to prepare a solid pharmaceutical composition of apremilast based on the teachings of the '052 publication would have consulted Brittain 1997 because this is an article related to methods characterizing polymorphs published in the well-respected Journal of Pharmaceutical Sciences, a mainstream journal in the field jointly published by the American Pharmaceutical Association and the American Chemical, which are the professional bodies in the field. DTX-98.1; Steed Tr. 1116:19-1117:5.

1475. Another prior art that would have motivated a POSA to conduct a routine polymorph screen is the guidelines published in 1999 by the International Council for Harmonization ("the ICH Guidelines"). SOF ¶ 142; DTX-128; Steed Tr. 1117:9-1118:12. The ICH Guidelines provided guidance to regulatory bodies in the U.S., Europe, and Japan, so that drug products would have similar regulations across these different jurisdictions. Steed Tr. 1117:9-17.

1476. A POSA motivated to prepare a solid pharmaceutical composition of apremilast based on the teachings of the '052 publication would have consulted the ICH Guidelines "because they give the guidelines by which ultimately that solid pharmaceutical composition will become a commercial medicine." Steed Tr. 1117:23-1118:3.

1477. The ICH Guidelines explicitly recognizes what was well-known in the art—the possibility of polymorphic forms in pharmaceutical compounds. DTX-128.12; Steed Tr. 1118:3-7. The ICH Guidelines recognizes another well-known principle—different polymorphs may have different physical properties, which in turn may impact the quality or performance of new drug products. DTX-128.12; Steed Tr. 1118:7-11. The ICH Guidelines thus reminds a POSA that it is important to specify the appropriate solid state of the new drug compound. DTX-128.12; Steed Tr. 1118:11-13. To this end, the ICH Guidelines explicitly instructs a POSA to "[c]onduct a polymorph screen on drug substance." DTX-128.28; Steed Tr. 1119:1-3.

1478. The prior art also teaches a POSA how to conduct a polymorph screen. For example, Guillory teaches various methods to isolate polymorphs and to devise a polymorph screen to prepare various solid forms of pharmaceutical compounds. DTX.125-7; Steed Tr. 1119:22-1120:11.

1479. Guillory teaches a POSA "what solvents they should incorporate within their polymorph screen." Steed Tr. 1120:25-1121:11. In particular, Guillory teaches "[i]n determining what solvents to use for crystallization, one should be careful to select those likely to be encountered during formulation and processing." DTX-125.14; *see also* Sacchetti Tr. 1169:24-1170:11-20 (polymorphic screening typically include solvents that are commonly used in pharmaceutical processing). Amgen's expert, Dr. Myerson agrees. Myerson Tr. 1628:3-6. "And processing includes making the drug substance in the first place so the synthesis procedure

like" those described in the '052 publication for preparing enantiomerically pure apremilast. Steed Tr. 1121:19-25.

1480. As explained above, the '052 publication discloses a specific solvent system used in the last step of preparing enantiomerically pure apremilast: a 2:1 mixture of ethanol to acetone used for purifying the crude apremilast residue. DTX-179.15 (¶ [0103]). Amgen's expert, Dr. Myerson agrees. Myerson Tr. 1628:7-11.

1481. Based on Guillory's teachings, a POSA would have understood that "the very most obvious first step within the polymorph screen is to include a screening based on the solvent ethanol and acetone." Steed Tr. 1122:12-25. Dr. Myerson agrees. Myerson Tr. 1631:4-10, 1631:20-25.

1482. A POSA would have understood the teachings of the '052 publication regarding the solvents as an important factor in "in determining polymorphic outcome." Steed Tr. 1122:25-1123:3. Therefore, a POSA in view of the '052 publication, Brittain 1997, the ICH Guidelines, and Guillory, would have been motivated to perform a polymorph screen on enantiomerically pure apremilast using ethanol and acetone as solvents.

1483. By 2008, a POSA would have known how to characterize various forms obtained from a polymorph screen of apremilast. There were several methods known in the art for characterizing different solid or crystalline forms obtained from a polymorph screen, including x-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and dynamic vapor sorption (DVS), solubility, melting point, or other techniques. Steed Tr. 1077:15:1078:11. XRPD, for example, was commonly used in the pharmaceutical industry "to determine what crystalline form has been made and to verify that a crystalline form is being made reproducibly." Myerson Tr. 429:21-25. The XRPD technique was

known to generate "effectively, a fingerprint of a particular polymorph form as long as it's a pure form," thus it was known to generate "a different pattern of peaks for each isolated pure form." Steed Tr. 1078:18-22.

1484. Chapter 6 written by Brittian in the book titled "Polymorphism in Pharmaceutical Solids" by Brittian published in 1999 ("Brittain 1999") describes XRPD as "the predominant tool," "eminently suited for the routine characterization of polymorphs." SOF ¶ 138; DTX-455.39.

1485. A POSA would have used these analytical techniques, including XRPD, to identify a polymorph and to distinguish it from other forms "by looking at the characterization data in total," to find out which forms obtained from a polymorph screen were pure and which ones were mixtures, and to determine unique forms obtained and label them with unique identifiers, such as Form A, Form B. Steed Tr. 1079:3-14.

1486. Therefore, a POSA would have been motivated to perform a routine polymorph screen on the known enantiomerically pure apremilast using the prior art disclosed ethanol and acetone as solvents, and identify and characterize the pharmaceutically relevant solid forms obtained in view of the '052 publication and the knowledge of a POSA, or alternatively in view of the '052 publication, Brittain 1997, the ICH Guidelines, Guillory, Brittain 1999, and the knowledge of a POSA.

2. A POSA Would Have Reasonably Expected To Successfully Prepare Pharmaceutically Relevant Solid Forms Of Apremilast, Including Form B, In A Polymorph Screen Using Known Solvents Ethanol And Aceton.

1487. As discussed above in Section VII.C.1, based on the teachings of the '052 publication, a POSA would have been motivated to perform a polymorph screen on the known enantiomerically pure apremilast using ethanol and acetone as solvents, which are disclosed in

the ’052 publication as the solvents used in the last step of synthesis and purification of apremilast.

1488. A POSA would have understood the solvent system taught in the ’052 publication is an important factor “in determining polymorphic outcome.” Steed Tr. 1122:25-1123:3. Indeed, Amgen’s expert, Dr. Myerson agrees that a POSA would have reasonably expected to succeed in carrying out a crystallization experiment using the solvent system described in Example 2 of the ’052 publication. Myerson Tr. 1633:6-14. Therefore, a POSA in view of the ’052 publication would have reasonably expected to prepare solid forms of apremilast, including apremilast crystalline Form B claimed in claims 1 and 15 of the ’101 patent. Steed Tr. 1126:14-18.

1489. Additionally, Guillory’s teachings further support a POSA’s reasonable expectation of success. Guillory explains that the methods it describes for performing a polymorph screen “should provide some assurance that the ‘due diligence’ has been exercised to isolate and identify crystalline forms that are likely to arise during the normal course of drug development and storage,” i.e., the pharmaceutically relevant forms. DTX-125.7; Steed Tr. 1119:22-1120:19, 1123:8-23 (“in the case of the forms disclosed by the ’101 patent, the forms of apremilast, in other words, a POSA would have every expectation of success in carrying out a screen based upon crystallization studies from a binary ethanol [] acetone solvent, as well as, of course, other common laboratory solvents. And they would -- they would expect that they would in that way identify the kinds of solid forms likely to be of relevance in pharmaceutical pre-formulation.”)

1490. Crystalline apremilast Form B claimed in claims 1 and 15 of the ’101 patent is a pharmaceutically relevant form that is “likely to arise during the normal course of drug

development and storage" because it was reported to be the "most thermodynamically stable anhydrous polymorph." Xu Tr. 541:23-542:7; *see also* Sacchetti Tr. 1188:1-2 ("Form B is a thermodynamically more stable form than Form A"). Thus, based on the teachings of the '052 publication and Guillory, a POSA would have reasonably expected to prepare pharmaceutically relevant solid forms of apremilast, including apremilast crystalline Form B claimed in claims 1 and 15 of the '101 patent. Steed Tr. 1126:4-6.

3. The Remaining Elements of Claims 1 and 15 of The '101 Patent Would Have Been Obvious.

1491. The remaining element of claim 1 that recites "an X-ray powder diffraction pattern comprising peaks at about 10.1, 13.5, 20.7, and 26.9 degrees 2θ," is obvious to a POSA in view of the prior art. It is undisputed that the XRPD peaks recited above are inherent characteristics of the pure apremilast crystalline Form B. Steed Tr. 1124:19-1125:7, 1126:20-24, 1127:6-8; Myerson Tr. 1587:20-22; Sacchetti Tr. 1168:7-11. As discussed above in Section VII.C.1, a POSA would have routinely performed the XRPD experimentation and observed the recited peaks following the preparation of Form B crystal form of enantiomerically pure apremilast in a routine polymorph screen. *See also* DTX-455.39 (describing XRPD as "the predominant tool," "eminently suited for the routine characterization of polymorphs.").

1492. The additional limitation of claim 15 that recites "a solid pharmaceutical composition" element is explicitly disclosed in the '052 publication. The '052 publication discloses "the incorporation of [apremilast] into pharmaceutical compositions and single unit dosage forms". DTX-179.7 (¶ [0032]); Steed Tr. 1113:18-1114:4; Sacchetti Tr. 1176:11-14 (the '052 publication teaches the utility of apremilast in treating certain diseases and disorders). The '052 publication discloses examples of single unit dosage forms of enantiomerically pure

apremilast, including those containing crystalline or amorphous solids. DTX-179.11 (¶ [0062]); Steed Tr. 1114:8-16.

1493. Therefore, claims 1 and 15 of the '101 patent would have been obvious as of March 27, 2008, in view of the '052 publication and the knowledge of a POSA, as well as in view of the '052 publication, Brittain 1997, the ICH Guidelines, Guillory, Brittain 1999, and the knowledge of a POSA.

4. Amgen Asserts No Objective Indicia Of Nonobviousness.

1494. At trial, Amgen did not present any evidence related to any alleged objective indicia of nonobviousness with respect to claims 1 and 15 of the '101 patent. Steed Tr. 1127:12-17.

VIII. Zydus Does Not Infringe the Asserted Claims of the '101 Patent.

A. Background

1. Analysis of Pharmaceutical Compounds

1600. Crystalline forms of organic compounds can be distinguished based on tests analyzing their physical properties. Miller Tr. 1221:11-1222:7; DDX-ZYDUS-4.5. X-ray Power Diffraction (XRPD) is the primary test for distinguishing polymorphic (crystalline) forms. Miller Tr. 1221:11-1222:7; DDX-ZYDUS-4.5. The diffractogram acts as a fingerprint for a crystal form. Miller Tr. 1222:10-1224:7; DDX-ZYDUS-4.6. Synchrotron X-ray Powder Diffraction (SXRPD) uses a high intensity x-ray source that cannot be produced by conventional laboratory equipment, is generally not used by pharmaceutical companies, and generates a diffractogram just like that from conventional XRPD equipment. Miller Tr. 1221:11-1222:7; DDX-ZYDUS-4.5. It is scientifically inaccurate to identify a crystal form using only one peak. Miller Tr. 1222:10-1224:7; DDX-ZYDUS-4.6.

2. Expiration Dates and Sample Storage

1601. All pharmaceutical products have storage, packaging, and handling instructions that ensure the product is safe and effective during its shelf life. Miller Tr. 1225:10-1226:16; DDX-ZYDUS-4.7. Instructions include expiration date and controlled storage conditions. Miller Tr. 1225:10-1226:16; DDX-ZYDUS-4.7; DTX-ZYDUS-24.2-3, Zydus Module 3.2.P.8.3 Stability Data; JTX-902.3-31, Zydus Certificates of Analysis—Drug Product.

1602. It is common knowledge that mold growing on expired bread cannot be blamed on the baker. Miller Tr. 1225:10-1226:16. Likewise, physicians do not prescribe, pharmacies do not dispense, and patients do not take expired pharmaceuticals. *Id.*

3. Zydus's Expert Witness

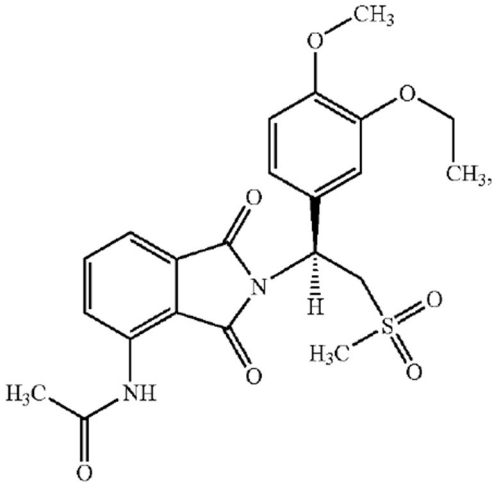
1603. Dr. Steven Miller is the president and owner of H&M Analytical Services. Miller Tr. 1216:17-20; DDX-ZYDUS-4.2; DTX-ZYDUS-9, Curriculum Vitae of Dr. Steven Miller ("Miller CV"). Dr. Miller has extensive experience with XRPD, including in the pharmaceutical context. Miller Tr. 1219:2-24; DTX-ZYDUS-9 (Miller CV). Dr. Miller has analyzed thousands of XRPD diffraction patterns and analyzes about 50 XRPD patterns per week. Miller Tr. 1219:2-1220:5. Dr. Miller was recognized without objection as an expert in characterization, identification and analysis of polymorphs. Miller Tr. 1220:17-23.

4. The Asserted Claims of the '101 Patent

1604. Asserted claims 1 and 15 of the '101 patent read:

1. A Form B crystal form of the compound of Formula (I):

(I)



which is enantiomerically pure, and which has an X-ray powder diffraction pattern comprising peaks at about 10.1, 13.5, 20.7, and 26.9 degrees 2θ.

15. A solid pharmaceutical composition comprising the crystal form of any one of claims 1 and 2 to 13.

Miller Tr. 1227:6-16; DDX-ZYDUS-4.9; JTX-5.67 (59:2-24, 60:28-29) ('101 Patent).

B. Amgen Has Failed to Prove Infringement Of The '101 Patent.

1605. Plaintiff's experts have failed to show that the apremilast in Zydus's proposed ANDA product more likely than not contains apremilast Form B as claimed and described in the '101 patent. Dr. Gozzo's testing presents no evidence that apremilast Form B is present in representative samples of Zydus's proposed ANDA product. Dr. Myerson has identified no Zydus internal document contradicting the conclusion that the apremilast in Zydus's proposed ANDA product is solely Form A.

1. Dr. Myerson and Dr. Gozzo Have Not Proven That Zydus's Proposed ANDA Product Would Infringe the Asserted Claims of the '101 Patent.

1606. Dr. Myerson and Dr. Gozzo have failed to present evidence that Zydus's proposed ANDA product more likely than not contains apremilast Form B. Miller Tr. 1227:22-1228:18; DDX-ZYDUS-4.11. Dr. Myerson bases his infringement opinions on Dr. Gozzo's test results

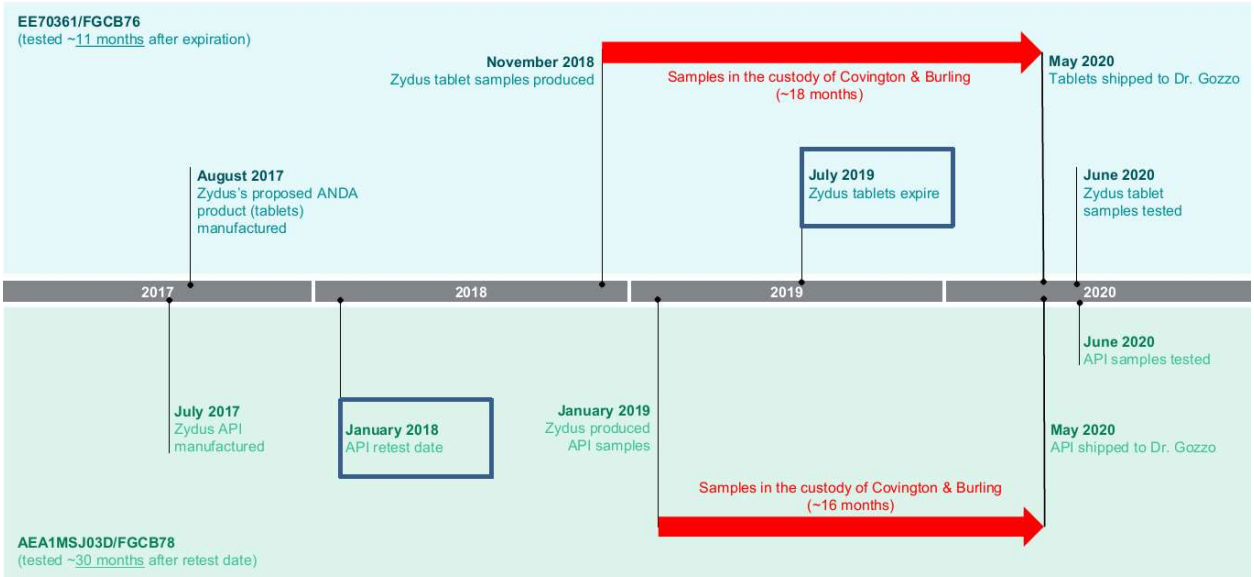
for expired samples that were not shown to be representative of what Zydus would sell. Gozzo Tr. 512:10-20; Miller Tr. 1227:22-1228:18; Myerson Tr. 472:11-19, 473:21-474:3, 476:25-477:2; DDX-ZYDUS-4.11; DTX-ZYDUS-24.3 (Zydus ANDA Product Stability Data); DTX-ZYDUS-29, Zydus ANDA Finished Product Shelf Life Specification – 30 mg ("Zydus ANDA Product Specification"); JTX-900.3-18, Zydus ANDA Section 3.2.S.4.4 February 2018 ("Zydus API COAs"); JTX-902.3-31 (Zydus ANDA Product COAs); JTX-910, Cadila DMF Module 3.2.S.4 Control of Drug Substance, Specification ("Zydus API Specification").

1607. Dr. Myerson cannot point to all four claimed peaks in Zydus's samples, failing to meet the standard for infringement. Miller Tr. 1227:22-1228:18; DDX-ZYDUS-4.11; JTX-5.5, 25, 46 (18:46-60), 50 (25:32-46), 67 (59:23-24) ('101 Patent); JTX-901.15-21, Zydus ANDA, Study Report - Polymorphic Evaluation of Apremilast in Drug Product ("Zydus ANDA Polymorph Report"); PTX-1238, Enlarged versions of experimental diffractograms for the samples analyzed (Gozzo Zydus Appendix C) ("Gozzo Diffractograms"); PTX-1241, Experimental peak list data for the samples analyzed (Gozzo Zydus Appendix E) ("Gozzo Peak Lists"). Dr. Myerson points to peaks in Zydus's samples that can be attributed to apremilast Form A and/or Form F. Miller Tr. 1227:22-1228:18; Myerson Tr. 444:1-446:24; DDX-ZYDUS-4.11; JTX-5.5, 25, 46 (18:46-60), 50 (25:32-46), 67 (59:23-24) ('101 Patent); PTX-1238 (Gozzo Diffractograms); PTX-1241 (Gozzo Peak Lists).

1608. It is uncontested that Zydus's internal testing on representative samples of Zydus's proposed ANDA product and apremilast API shows apremilast Form A. Miller Tr. 1227:22-1228:18; Myerson Tr. 468:2-6; DDX-ZYDUS-4.11; JTX-901.15-21 (Zydus ANDA Polymorph Report).

2. Zydus's Proposed ANDA Product and API Samples Were Tested Past Expiration/Retest.

1609. The image below depicts the timeline of events that demonstrate some of the logistical failures on the part of Plaintiff that prevented Dr. Gozzo from ever having access to representative samples of Zydus's proposed ANDA product and API. Gozzo Tr. 511:21-24; Miller Tr. 1229:10-1230:23; DDX-ZYDUS-4.12; DTX-ZYDUS-24.3 (Zydus ANDA Product Stability Data); JTX-900.9 (Zydus API COAs); JTX-902.26 (Zydus ANDA Product COAs); PTX-1115.1-4, Declaration of Marissa Golub Regarding Chain of Custody of API, ANDA Product, and Excipient Samples, dated November 23, 2020 (Zydus) ("Golub Declaration").



1610. The samples that Dr. Gozzo tested were expired. Miller Tr. 1229:10-1230:23; Myerson Tr. 468:17-469:3, 473:21-474:3; DDX-ZYDUS-4.11-13; DTX-ZYDUS-24.3 (Zydus ANDA Product Stability Data); JTX-900.3-18 (Zydus API COAs); JTX-902.3-31 (Zydus ANDA Product COAs); PTX-1115.1-4 (Golub Declaration). It is undisputed that there was a large temporal gap between the date on which Plaintiff received samples of Zydus's proposed ANDA product and API and the dates of Dr. Gozzo's testing. Gozzo Tr. 511:21-24; Miller Tr. 1229:10-1230:23; Myerson Tr. 474:7-12; DDX-ZYDUS-4.11-13; DTX-ZYDUS-24.3 (Zydus ANDA

Product Stability Data); JTX-900.3-18 (Zydus API COAs); JTX-902.3-31 (Zydus ANDA Product COAs); PTX-1115.1-4 (Golub Declaration). Amgen waited more than ten months after the tablets expired before they arranged to ship the tablets to Dr. Gozzo, who tested the tablets about a month later. Gozzo Tr. 511:21-24; Miller Tr. 1229:10-1230:23; Myerson Tr. 468:17-469:3, 474:7-12; DDX-ZYDUS-4.11-13; DTX-ZYDUS-24.3 (Zydus ANDA Product Stability Data); JTX-900.3-18 (Zydus API COAs); JTX-902.3-31 (Zydus ANDA Product COAs); PTX-1115.1-4 (Golub Declaration). Therefore, Zydus's proposed ANDA product and API samples were tested at least two and a half years and more than ten months past their retest/expiration dates, respectively. Gozzo Tr. 511:21-24; Miller Tr. 1229:10-1230:23; Myerson Tr. 472:3-8, 476:4-10; DDX-ZYDUS-4.11-13; DTX-ZYDUS-24.3 (Zydus ANDA Product Stability Data); JTX-900.3-18 (Zydus API COAs); JTX-902.3-31 (Zydus ANDA Product COAs); PTX-1115.1-4 (Golub Declaration).

3. The Apremilast Samples Tested by Dr. Gozzo Are Not Representative of Zydus's Proposed ANDA Product.

1611. At trial, Dr. Miller presented unrebutted evidence that none of the samples of Zydus's proposed ANDA product tested by Dr. Gozzo were representative of what Zydus would eventually sell. Gozzo Tr. 512:10-20; Miller Tr. 1231:2-1232:10; Myerson Tr. 474:13-475:8, 476:25-477:6; DDX-ZYDUS-4.13; DTX-ZYDUS-24.3 (Zydus ANDA Product Stability Data); DTX-ZYDUS-29 (Zydus ANDA Product Specification); JTX-900.3-18 (Zydus API COAs); JTX-902.3-31 (Zydus ANDA Product COAs); JTX-910 (Zydus API Specification); PTX-1115.1-2 (Golub Declaration). No Amgen expert tested Zydus's expired samples to determine whether they met Zydus's specifications and thus might be representative. Gozzo Tr. 512:10-20; Miller Tr. 1231:2-1232:7; Myerson Tr. 474:13-474:8; DDX-ZYDUS-4.13; DTX-ZYDUS-29 (Zydus ANDA Product Specification); JTX-910 (Zydus API Specification).

1612. The API and proposed ANDA product samples tested were at least two and a half years and more than ten months past their retest/expiration dates, respectively. Miller Tr. 1231:2-1232:7; Myerson Tr. 476:4-17; DDX-ZYDUS-4.12-13; DTX-ZYDUS-24.3 (Zydus ANDA Product Stability Data); JTX-900.3-18 (Zydus API COAs); JTX-902.3-31 (Zydus ANDA Product COAs); PTX-1115.1-2 (Golub Declaration). Amgen's counsel received Zydus's samples approximately eighteen months before testing was undertaken and more than six months prior to ANDA product sample expiration. Miller Tr. 1231:2-1232:7; Myerson Tr. 474:7-12, 476:4-17; DDX-ZYDUS-4.13; DTX-ZYDUS-24.3 (Zydus ANDA Product Stability Data); JTX-900.3-18 (Zydus API COAs); JTX-902.3-31 (Zydus ANDA Product COAs); PTX-1115.1-2 (Golub Declaration). Amgen and its counsel provided no information concerning the specific storage conditions for Zydus's samples over the eighteen months they were stored in law offices at ambient humidity. Gozzo Tr. 512:3-6; Miller Tr. 1231:2-1232:7; Myerson Tr. 469:4-20, 475:19-21; DDX-ZYDUS-4.13. Amgen has provided no reason why samples that were received well in advance of expiration were not tested until well after expiration. Miller Tr. 1231:2-1232:7; Myerson Tr. 476:18-24; DDX-ZYDUS-4.13. Amgen's counsel could have had the samples tested before they were expired. Myerson Tr. 476:18-20.

1613. No conclusions can be drawn from Dr. Gozzo's testing because there is no evidence that the samples tested were representative of Zydus's proposed ANDA product or API. Miller Tr. 1231:2-1232:7; Myerson Tr. 474:13-475:8, 476:25-477:2; DDX-ZYDUS-4.13; DTX-ZYDUS-24.3 (Zydus ANDA Product Stability Data); DTX-ZYDUS-29 (Zydus ANDA Product Specification); JTX-900.3-18 (Zydus API COAs); JTX-902.3-31 (Zydus ANDA Product COAs); JTX-910 (Zydus API Specification); PTX-1115.1-2 (Golub Declaration).

4. Dr. Gozzo's Testing Fails to Establish the Presence of the Claimed Form B in Zydus's Proposed ANDA Product.

1614. Samples of expired tablets do not show peaks at two of four locations required by claims 1 and 15: (1) no peaks at 20.7 and 26.9 ± 0.2° 2θ; (2) peaks at 10.1 and 13.5 ± 0.2° 2θ should be attributed to Form A. Miller Tr 1232:14-1233:7; Myerson Tr. 483:1-7; DDX-ZYDUS-4.14; JTX-5.5, 9, 25, 46 (18:46-60), 47 (20:13-27), 50 (25:32-46), 67 (59:2-24, 60:29-30) ('101 Patent); JTX-902.3-31 (Zydus ANDA Product COAs); PTX-1238.18-19, 38-39 (Gozzo Diffractograms).

1615. In the following diffractograms, the green patterns represent Zydus's proposed ANDA product, the black lines represent Zydus's API, the red lines represent the Form A reference standard, and the blue patterns represent the Form B reference standard. Miller Tr. 1235:2-13; Myerson Tr. 466:18-467:17, 482:20-22; PTX-1238 (Gozzo Diffractograms).

1616. As depicted below, there is plainly no peak at 20.7 ± 0.2° 2θ in any of the samples of Zydus's proposed ANDA product. Miller Tr. 1233:14-1235:1; Myerson Tr. 483:1-3; PTX-1238.39 (Gozzo Diffractograms). Dr. Gozzo's own blue vertical dotted line gives a clear demonstration of where any peak at 20.7 ± 0.2° 2θ would have been in Zydus's proposed ANDA product. Miller Tr. 1233:14-1235:1; PTX-1238.39 (Gozzo Diffractograms). Instead of a peak, there is nothing. Miller Tr. 1233:14-1235:1; Myerson Tr. 483:1-3; PTX-1238.39 (Gozzo Diffractograms). While there is no peak at 26.9 ± 0.2° 2θ in the samples of Zydus's proposed ANDA product, the peak to the left and other peak to the right of the blue vertical dotted line unequivocally matches the Form A peak near that location, not the Form B peak. Miller Tr. 1235:15-1236:12; Myerson Tr. 480:11-13; PTX-1238.39 (Gozzo Diffractograms). Dr. Gozzo never performed spiking studies to support Dr. Myerson's bald assertion that Form B was somehow contributing to these peaks. Myerson Tr. 481:19-24. Dr. Gozzo's own blue vertical

dotted line gives a clear demonstration of how the peak in Zydus's proposed ANDA product matches with Form A, not Form B. Miller Tr. 1235:15-1236:12; PTX-1238.39 (Gozzo Diffractograms)

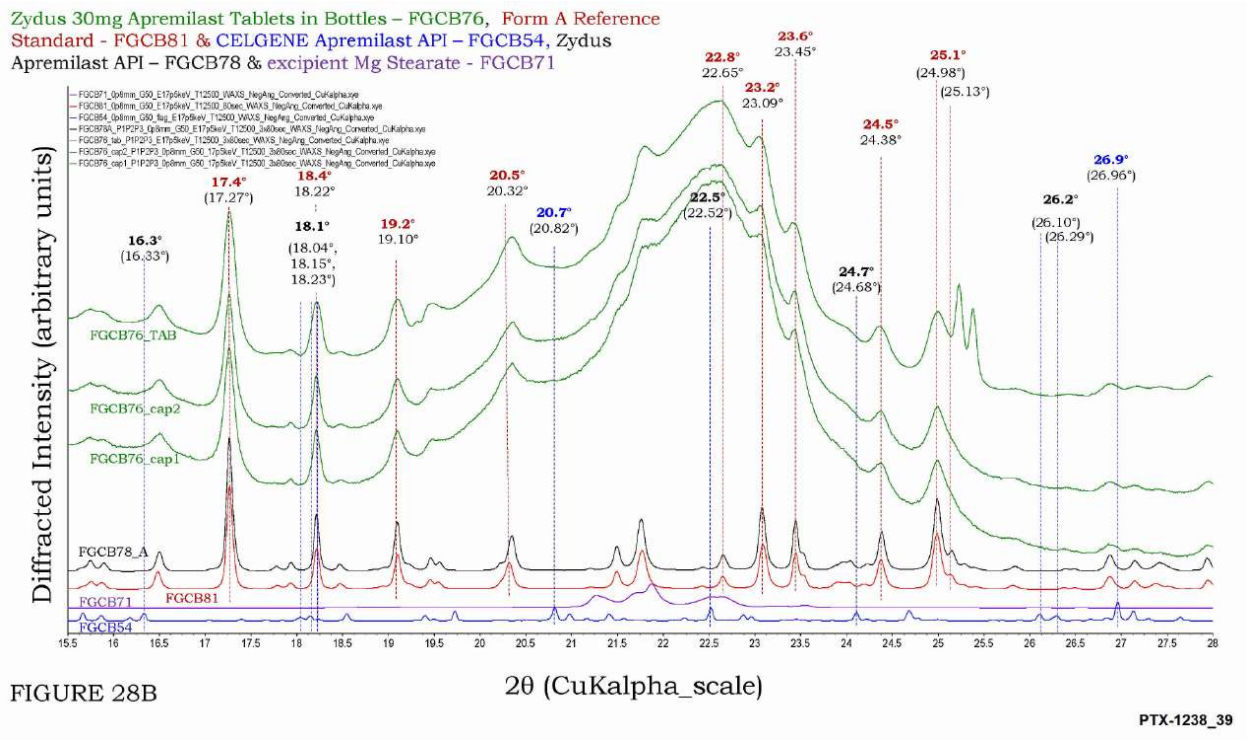
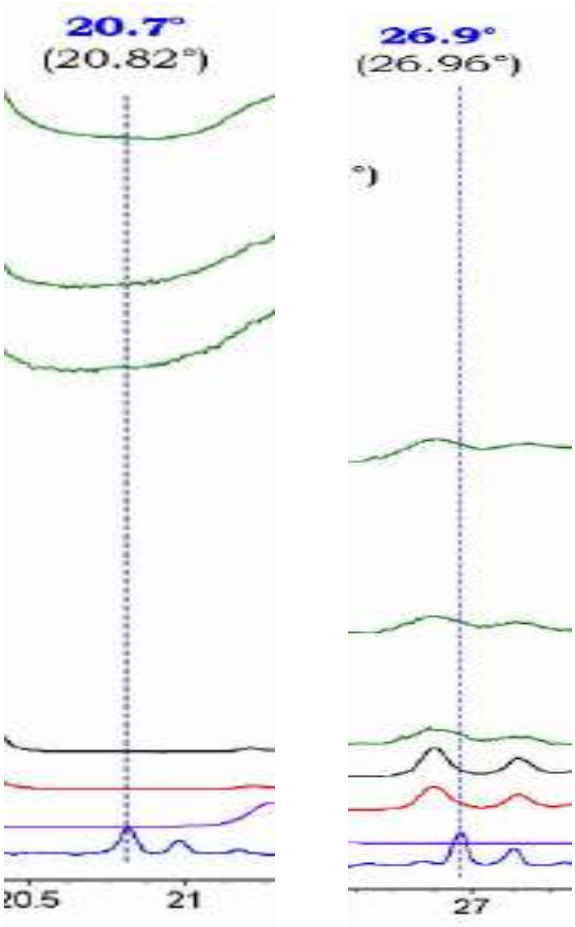


FIGURE 28B

PTX-1238_39



1617. As depicted below, the peaks at 10.1 and 13.5 ± 0.2° 2θ should be attributed to Form A. Miller Tr. 1241:9-1243:15; PTX-1238.38 (Gozzo Diffractograms). The absence of Form B is highlighted by the fact that Zydus's proposed ANDA products do not display the "doublet" at 13.5 ± 0.2° 2θ. Miller Tr. 1242:18-1243:15; PTX-1238.38 (Gozzo Diffractograms).

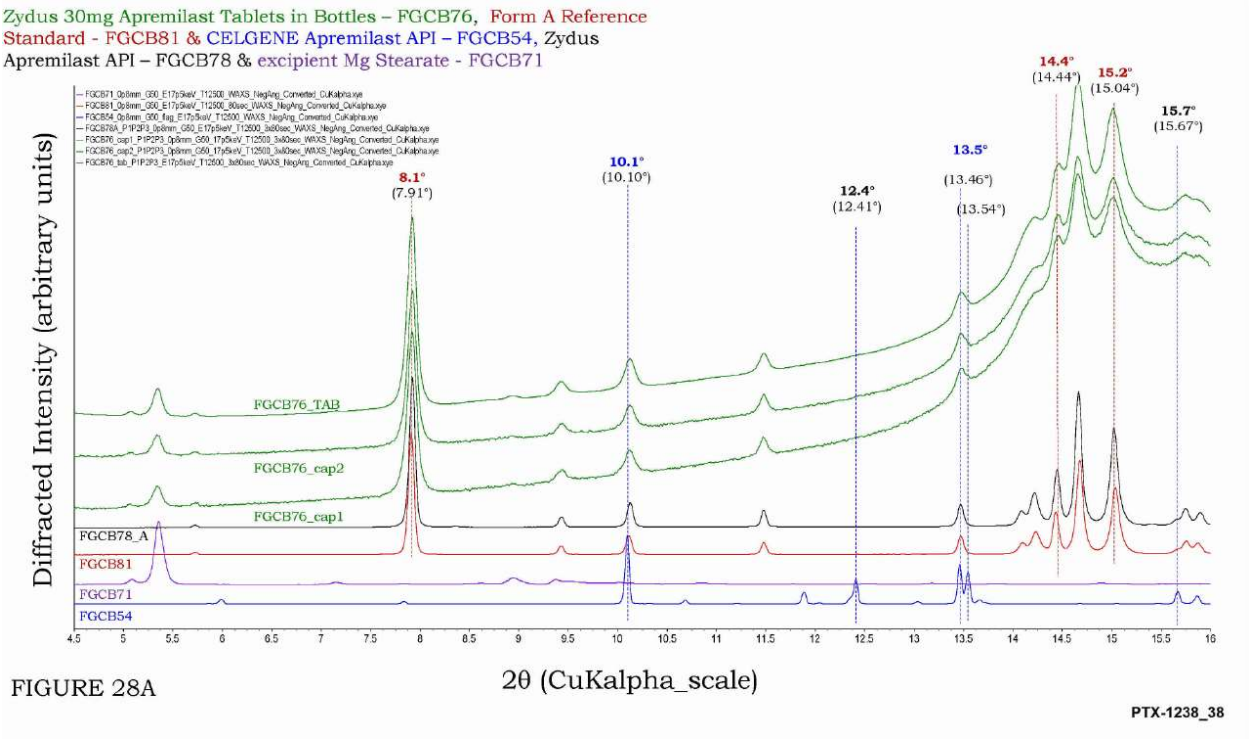
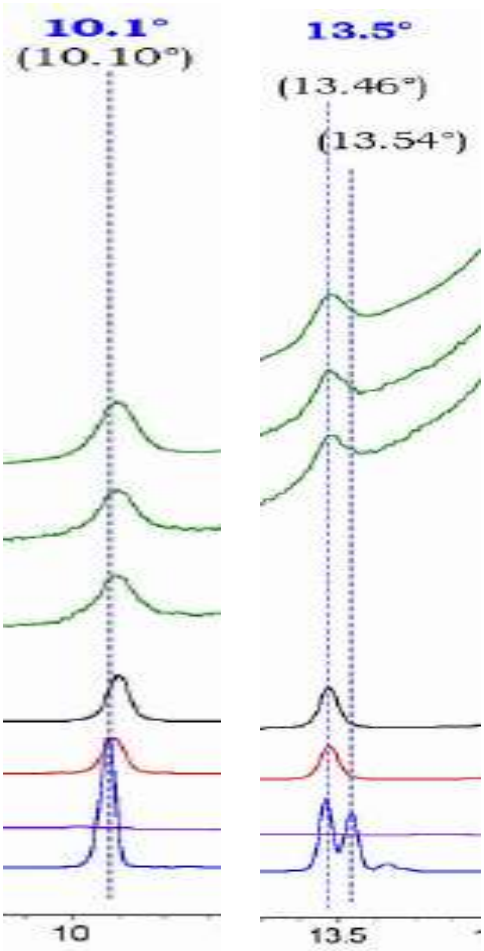

Zydus 30mg Apremilast Tablets in Bottles – FGCB76, Form A Reference
Standard - FGCB81 & CELGENE Apremilast API – FGCB54, Zydus
Apremilast API – FGCB78 & excipient Mg Stearate - FGCB71
Diffracted Intensity (arbitrary units)
8.1° (7.91°)
10.1° (10.10°)
12.4° (12.41°)
13.5° (13.46°) (13.54°)
14.4° (14.44°)
15.2° (15.04°)
15.7° (15.67°)
FGCB76_TAB
FGCB76_cap2
FGCB76_cap1
FGCB78_A
FGCB81
FGCB71
FGCB54
2θ (CuKalpha_scale)
PTX-1238_38

FIGURE 28A


10.1° (10.10°)
13.5° (13.46°) (13.54°)
10
13.5

1618. Peaks cannot be "hidden" as Dr. Myerson suggests—they are either present or not present. Miller Tr. 1240:18-25, 1268:24-1269:14 ("[I]f there's no peak present, the conclusion is it's not there. And that's definitive. That's the whole point of limit of detection. . . . [Y]ou're not looking at mixtures [where] you know what's in it. You're looking at something that you don't know what's in it, and that's the entire point of limit of detection.").

1619. At trial, Dr. Myerson provided no testimony that Dr. Gozzo's testing of Zydus's proposed ANDA products showed any evidence of Form B. Miller Tr. 1236:21-24; Myerson Tr. 467:23-468:1.

1620. Samples of expired drug substance do not show a peak at one of four locations required by claims 1 and 15: (1) no peak at 26.9 ± 0.2° 2θ; (2) any purported feature at 20.7 ± 0.2° 2θ can be attributed to Form F; and (3) peaks at 10.1 and 13.5 ± 0.2° 2θ should be attributed to Form A. Miller Tr. 1243:19-1244:1; DDX-ZYDUS-4.14; JTX-5.5, 9, 25, 46 (18:46-60), 47 (20:13-27), 50 (25:32-46), 67 (59:2-24, 60:29-30) ('101 Patent); JTX-900.3-18 (Zydus API COAs); PTX-1238.18-19, 38-39 (Gozzo Diffractograms).

1621. As depicted below, the peaks to the left and to the right of the 26.9 ± 0.2° 2θ location in the samples of Zydus's API unequivocally matches the Form A peaks near that location, not the Form B peak. Miller Tr. 1245:13-1246:12; PTX-1238.19 (Gozzo Diffractograms). Dr. Gozzo's own blue vertical dotted line gives a clear demonstration of how the peak in Zydus's API matches with Form A, not Form B. Miller Tr. 1245:13-1246:12; PTX-1238.19 (Gozzo Diffractograms). Amgen has done no statistical analysis to prove that the little bump at 20.7 ± 0.2° 2θ in any of the samples of Zydus's API. Miller Tr. 1244:9-1245:12; PTX-1238.19 (Gozzo Diffractograms). Neither has Amgen done any testing or analysis to exclude the possibility that, assuming the little bump at 20.7 ± 0.2° 2θ is attributable to Form F, which shows

a peak at 20.7 ± 0.2° 2θ. Miller Tr. 1244:9-1245:12; JTX-5.25, 41 (8:1-2), 50 (25:32-46) ('101 Patent); PTX-1238.19 (Gozzo Diffractograms).

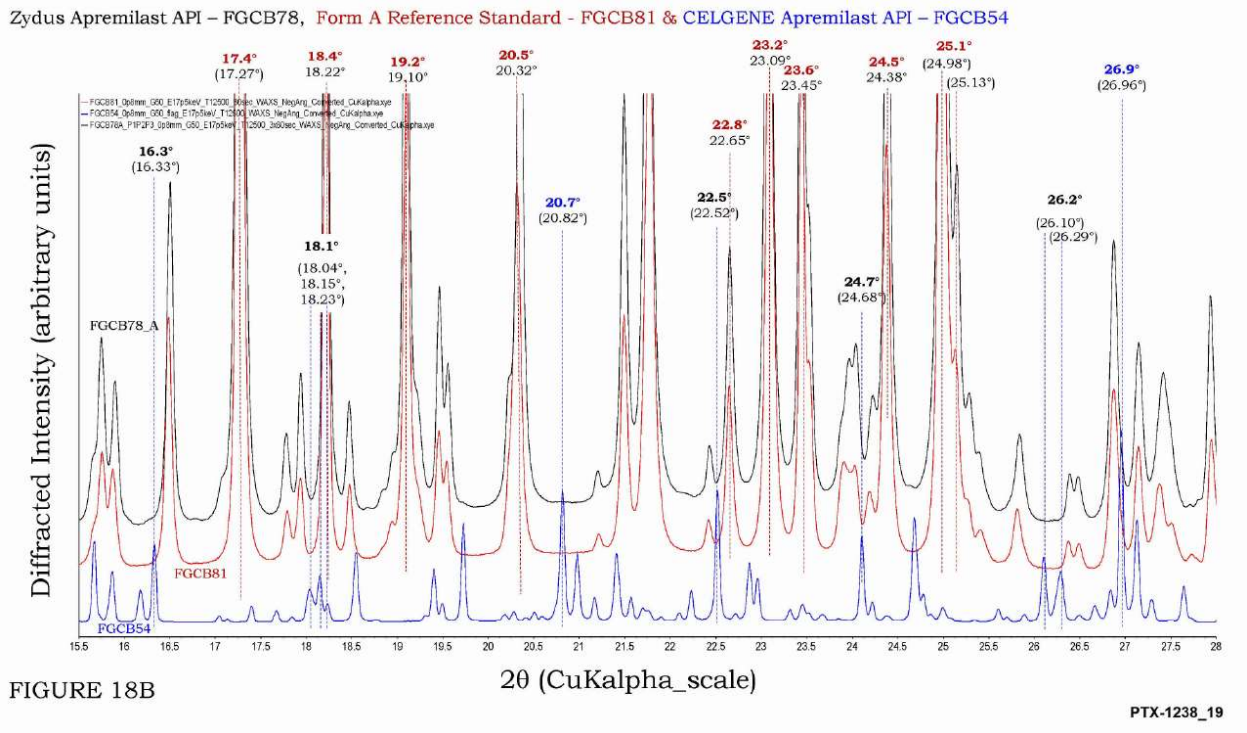


FIGURE 18B

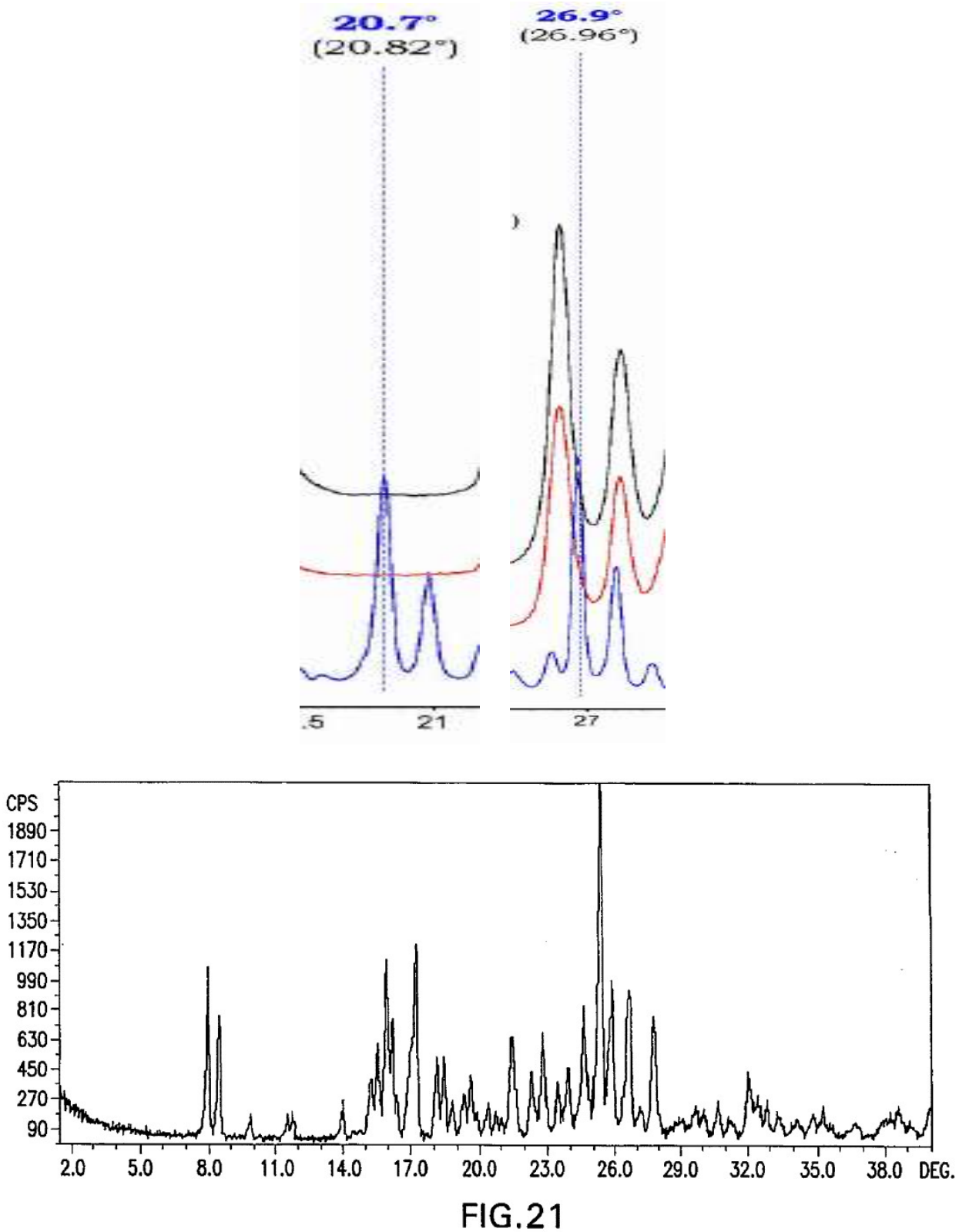

20.7°
(20.82°)
26.9°
(26.96°)
.5
21
27
CPS
1890
1710
1530
1350
1170
990
810
630
450
270
90
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
DEG.

FIG.21

1622. As depicted below, the peaks at 10.1 and 13.5 ± 0.2° 2θ should be attributed to Form A. Miller Tr. 1246:20-1248:22; PTX-1238.18 (Gozzo Diffractograms). The absence of Form B is highlighted by the fact that Zydus's API does not display the "doublet" at 13.5 ± 0.2° 2θ. Miller Tr. 1247:22-1248:22; PTX-1238.18 (Gozzo Diffractograms).

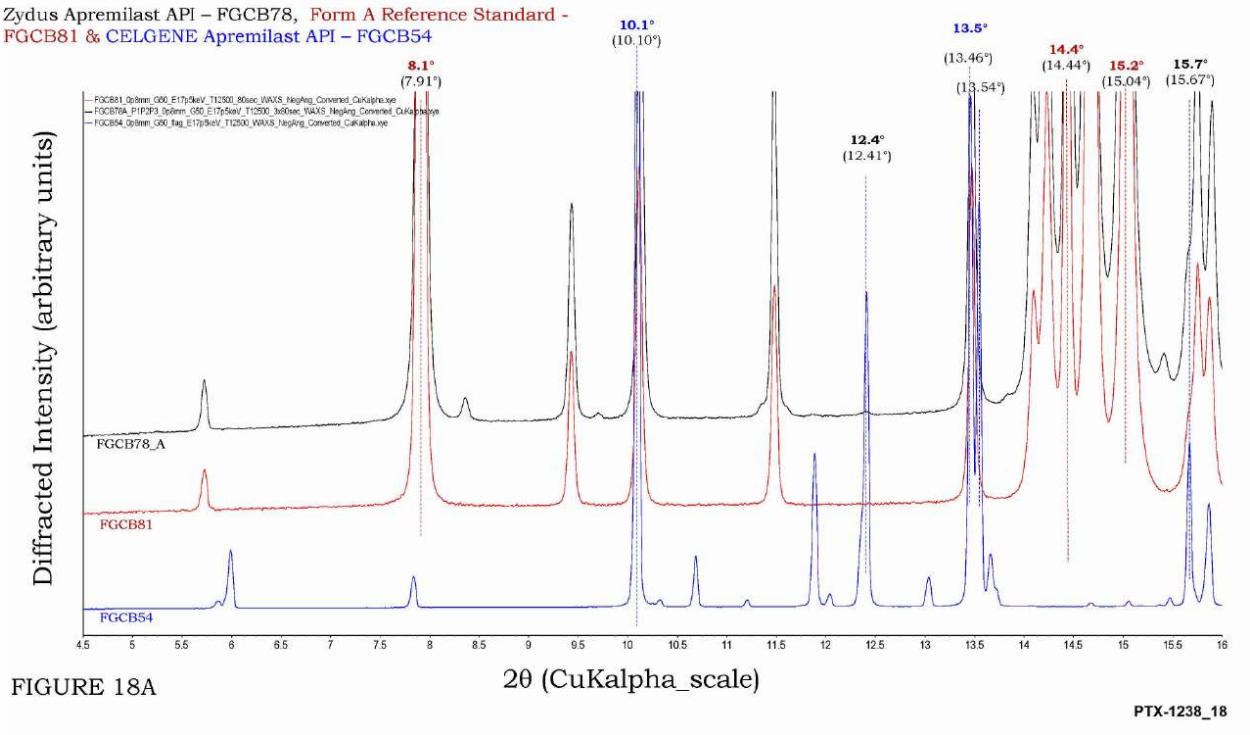
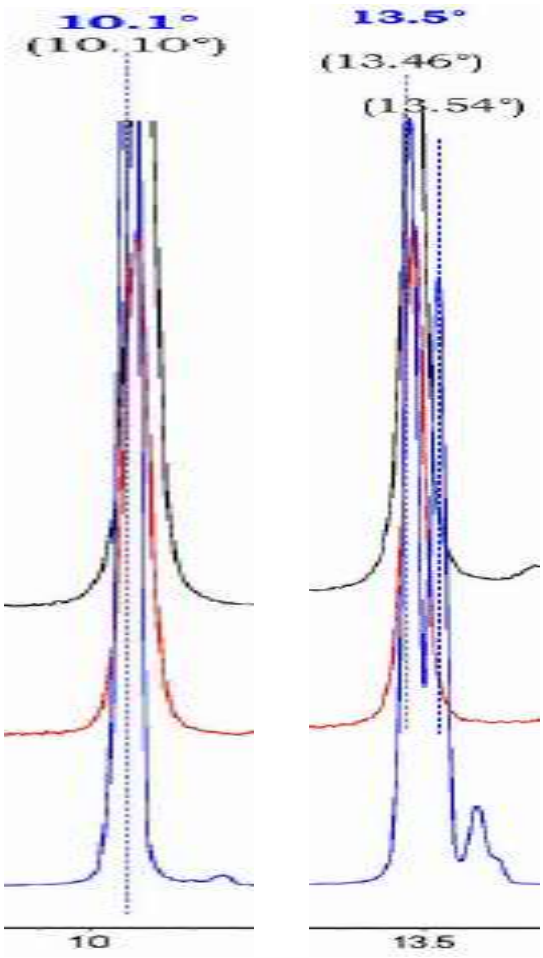
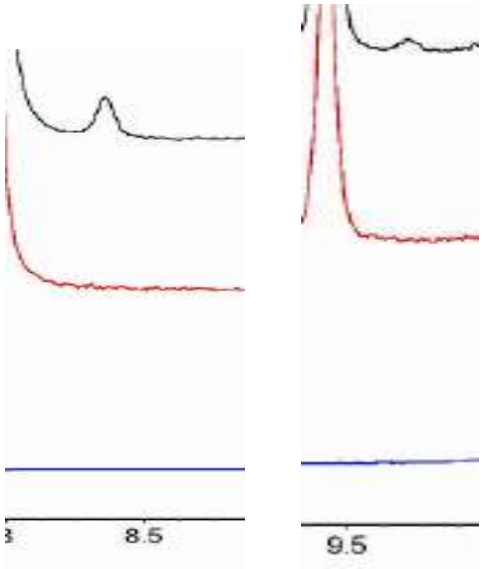


FIGURE 18A



1623. It is scientifically inaccurate to identify a polymorph based on a single peak (or even two peaks) in a diffractogram. Miller Tr. 1248:24-1249:24; DDX-ZYDUS-4.14. Neither Dr. Gozzo nor Dr. Myerson did any analysis to rule out crystalline forms other than Form A and Form B in the samples tested by Dr. Gozzo. Miller Tr. 1248:24-1249:24; DDX-ZYDUS-4.14 In fact, there are eight peaks in Zydus's API samples tested by Dr. Gozzo that do not appear in either the Form A or Form B reference standard. Miller Tr. 1248:24-1251:2; DDX-ZYDUS-4.14; PTX-1238.18 (Gozzo Diffractograms). Two of these eight peaks are depicted below.



Miller Tr. 1248:24-1251:2; PTX-1238.18 (Gozzo Diffractograms).

1624. It would be scientifically inaccurate to attribute peaks to Form B that are coincident with other forms of apremilast and scientifically inaccurate to attribute peaks characteristic of Form A to Form B. Miller Tr. 1251:6-16; DDX-ZYDUS-4.14. It would be inappropriate to conclude Form B, as described in claim 1 of the '101 patent, is present in Zydus's proposed ANDA product without all four claimed peaks. DDX-ZYDUS-4.14.

1625. Dr. Miller created a chart comparing peaks the '101 patent attributes to Form A, Form B, and Form F with peaks from Dr. Gozzo's testing of three samples of Zydus's API. Miller Tr. 1252:18-1253:6; DDX-ZYDUS-4.15; JTX-5.5, 9, 25, 46 (18:46-60), 47 (20:13-27), 50 (25:32-46) ('101 Patent); PTX-1241.6, 8, 10 (Gozzo Peak Lists). The yellow highlighting indicates where a Form B peak overlaps with a peak from Dr. Gozzo's SXRPD testing of the Form A reference standard, the green highlighting indicates where a Form A or Form F peak overlaps with a peak from the Form B reference standard, and the blue highlighting indicates where a Form B peak overlaps with a Form F peak as depicted in the '101 patent. Miller Tr.

1253:7-1255:16; DDX-ZYDUS-4.15; JTX-5.5, 9, 25, 46 (18:46-60), 47 (20:13-27), 50 (25:32-46) ('101 Patent); PTX-1241.6, 8, 10 (Gozzo Peak Lists).

'101 patent peaks

Peaks from Dr. Gozzo's testing

Listed Peaks					
Form A	Form B	Form F	Sample 078	Sample 079	Sample 080
8.1		8.1	7.9	7.9	7.9
		8.6	8.4	8.4	8.4
	10.1 (Overlap with Form A)		10.1	10.1	10.1
	12.4		12.4	12.4	12.4
	13.5 (Overlap with Form A)		13.4	13.5	13.5
14.4			14.4	14.5	14.5
15.2			15	15	15
	15.7 (Overlap with Form A)	15.6	15.7	15.7	15.7
	16.3 (Overlap with Form A)		16.5	16.5	16.5
17.4		17.3	17.3	17.3	17.3
	18.1 (Overlap with Form A)		18.2	18.2	18.2
18.4			18.4	18.5	18.5
19.2		19.3	19.2	19.2	19.2
20.5			20.3	20.3	20.3
	20.7 (Overlap withForm F)		20.8	20.8	20.8
		21.4	21.4	21.4	21.5
	22.5 (Overlap with Form A)		22.4	22.4	22.4
22.8		22.8	22.7	22.7	22.7
23.2			23.1	23.1	23.1
23.6			23.5	23.5	23.5
24.5	24.7 (Overlap with Form A)	24.6	24.6	24.7	24.7
25.1			25.1	25.1	25.1
		25.4	25.4	25.4	25.4
		25.9	25.8	25.9	25.8
	26.2 (Overlap with Form A)		26.4	26.4	26.4
		26.6	26.5	26.5	26.5
	26.9 (Overlap with Form A)		26.9	26.9	26.9
		27.7	27.7	27.7	27.7
	29.1 (Overlap with Form A)		29.1	29.1	29.1

	common with synchotron of Form B Sample (within +/- 0.2)
	common with synchotron of Form A Sample (within +/- 0.2)
	feature appears in Fig. 21 (Form F) (within +/- 0.2)

1626. Dr. Miller's chart shows that the peaks at 10.1, 13.5, 15.7, 16.3, 18.1, 22.5, 24.7, 26.2, 26.9, and 29.1 ± 0.2° 2θ are attributable to Form A. Miller Tr. 1253:7-1255:16 ("When you know something is present, you have to attribute the peaks to that -- to that phase or that compound first, and then you go look for other things."); DDX-ZYDUS-4.15; JTX-5.5, 9, 25, 46 (18:46-60), 47 (20:13-27), 50 (25:32-46) ('101 Patent); PTX-1241.6, 8, 10 (Gozzo Peak Lists). Further, the peaks at 8.4 and 20.7 ± 0.2° 2θ may be attributed to Form F. Miller Tr. 1253:7-

1255:16; DDX-ZYDUS-4.15; JTX-5.5, 9, 25, 46 (18:46-60), 47 (20:13-27), 50 (25:32-46) ('101 Patent); PTX-1241.6, 8, 10 (Gozzo Peak Lists).

1627. Dr. Gozzo never performed SXRPD testing of Form F reference standard for comparison. Gozzo Tr. 512:23-513:4; Miller Tr. 1253:7-1255:16; Myerson Tr. 483:13-15; DDX-ZYDUS-4.15; JTX-5.5, 9, 25, 46 (18:46-60), 47 (20:13-27), 50 (25:32-46) ('101 Patent); PTX-1241.6, 8, 10 (Gozzo Peak Lists). In fact, Amgen never provided Dr. Gozzo with any crystalline apremilast Form F to test. Gozzo Tr. 513:1-4. Neither did Dr. Gozzo perform SXRPD testing of any of the four other crystalline forms of apremilast identified in the '101 patent. Miller Tr. 1255:21-1256:3; JTX-5.41 (7:27-8:19) ('101 patent). Dr. Myerson has no way of knowing whether any of the peaks he attempts to attribute to Form B would have also been attributable to Form F had Dr. Gozzo performed synchrotron testing of Form F. Myerson Tr. 483:16-22.

1628. The significant overlap between the diffractograms and peak lists of Forms A, B, and F renders it impossible to conclude that Form B is present based on the evidence. Miller Tr. 1266:5-8 ("I can't really rule out anything because there wasn't sufficient analysis to really come to any kind of conclusion."). The potential for other crystalline forms of apremilast to be present in these expired samples further confounds this analysis. Miller Tr. 1265:20-1266:1; *see also* ¶ 1623.

1629. Despite having the capacity to do so, Dr. Gozzo never performed any testing to determine the synchrotron limit of detection for Form B in a sample of mostly Form A. Myerson Tr. 478:2-5. Dr. Myerson never offered any opinion as to what this limit of detection may have been. Myerson Tr. 478:6-11.

5. Zydus's Internal Testing Shows that Zydus's Proposed ANDA Product Does Not Infringe the Asserted Claims.

1630. Zydus's API specification requires five Form A XRPD peaks. JTX-910.6 (Zydus API Specification)

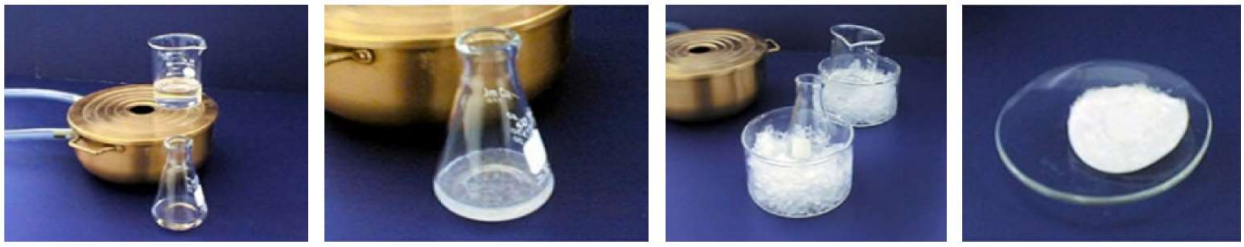
1631. Zydus's internal documents describe the only documented tests conducted on representative, unexpired samples of Zydus's apremilast API and proposed ANDA product. Miller Tr. 1256:7-19; Myerson Tr. 484:14-17; DDX-ZYDUS-4.16; JTX-900.3-18 (Zydus API COAs); JTX-901.15-21 (Zydus ANDA Polymorph Report); JTX-902.3-31 (Zydus ANDA Product COAs). Dr. Miller and Dr. Myerson agree that the only testing on representative, unexpired samples showed Form A apremilast, and Dr. Myerson does not contend that these tests showed Form B. Miller Tr. 1256:20-23; Myerson Tr. 467:23-468:9; DDX-ZYDUS-4.16; JTX-5.5, 46 (18:46-60) ('101 Patent); JTX-900.3-18 (Zydus API COAs); JTX-901.15-21 (Zydus ANDA Polymorph Report); JTX-902.3-31 (Zydus ANDA Product COAs). Dr. Miller confirmed that Zydus's internal testing confirms Zydus's noninfringement of the '101 patent. Miller Tr. 1227:22-1228:18, 1256:10-19. In forming his opinions, Dr. Myerson ignored Zydus's internal testing. Miller Tr. 1256:7-19; Myerson Tr. 467:23-468:9; DDX-ZYDUS-4.16.

IX. The Asserted Claims Of The '283 Patent Are Invalid.

A. Background

1. Crystallization from a Solvent

1700. Crystals are commonly produced by dissolving a compound in a single liquid solvent or mixture of solvents and then cooling. Sacchetti Tr. 1166:20-1167:17; DDX-ZYDUS-3.5. This process includes: (1) dissolving the compound using a steam bath; (2) allowing the solution to cool until crystals form; (3) further cooling for additional crystallization; and (4) isolating crystals by filtration. Sacchetti Tr. 1166:20-1167:17; DDX-ZYDUS-3.5.



2. Inherent Properties

1701. Inherent properties are physical and chemical properties that are inseparable from the polymorph itself and result from its unique structure. Sacchetti Tr. 1167:21-1168:1; DDX-ZYDUS-3.6; DTX-ZYDUS-8, Raj Suryanarayanan, *X-Ray Powder Diffractometry*, *in* PHYSICAL CHARACTERIZATION OF PHARMACEUTICAL SOLIDS (Harry G. Brittain ed., 1995) ("Suryanarayanan"); DTX-457.2, John Haleblian & Walter McCrone, *Pharmaceutical Applications of Polymorphism*, 58 J. PHARM. SCI. 911 (1969) ("Haleblian"). Such inherent properties include melting point and X-ray Powder Diffraction (XRPD) pattern and peaks. Sacchetti Tr. 1168:2-11; DDX-ZYDUS-3.6; DTX-ZYDUS-8 (Suryanarayanan); DTX-457.2 (Haleblian). The XRPD pattern is a unique inherent property of a polymorph. Sacchetti Tr. 1168:19-1169:5; DDX-ZYDUS-3.7; DTX-ZYDUS-7.5-6, *X-ray Diffraction*, *in* THE UNITED STATES PHARMACOPEIA 25 (2002) ("USP").

3. Polymorph Screening

1702. Polymorph screening is routine in the pharmaceutical industry for several reasons. Sacchetti Tr. 1169:13-1170:10; DDX-ZYDUS-3.8. The inherent solid state properties of polymorphs results generally in differences in manufacturability, stability, and bioavailability. Sacchetti Tr. 1169:13-1170:10; DDX-ZYDUS-3.8. FDA and other regulatory agencies have guidance documents to instruct pharmaceutical manufacturers to evaluate polymorphism because different polymorphs may exhibit different clinical efficacy and safety. Sacchetti Tr. 1169:13-1170:10; DDX-ZYDUS-3.8. The polymorphic form must be controlled and is typically part of

the drug substance specification. Sacchetti Tr. 1169:13-1170:10; DDX-ZYDUS-3.8. Polymorph screening typically involves crystallization from solvents commonly used in pharmaceutical processing. Sacchetti Tr. 1170:11-20; DDX-ZYDUS-3.8. Common techniques include cooling, evaporation, and antisolvent addition. Sacchetti Tr. 1170:11-20; DDX-ZYDUS-3.8; DTX-ZYDUS-7.5 (USP); DTX-102.4, Stephen Byrn et al., *Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations*, 12 PHARM. RES. 945 (1995) ("Byrn 1995"); DTX-125.9-16, J. Keith Guillory, *Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids*, *in* POLYMORPHISM IN PHARMACEUTICAL SOLIDS (Harry G. Brittain ed., 1999) ("Guillory").

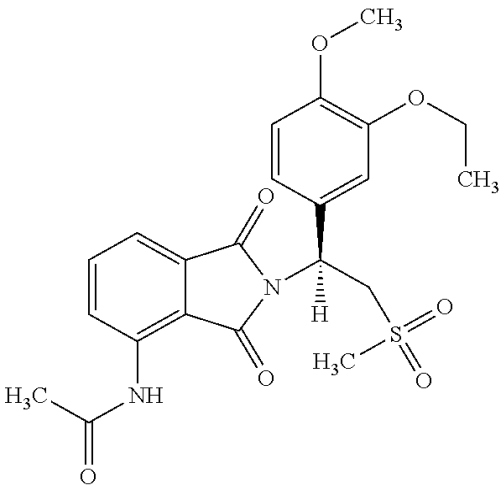
4. Zydus's Expert Witness

1703. Dr. Mark Sacchetti has significant experience in the pharmaceutical industry and is the scientific director of the Lenor Zeeh Pharmaceutical Experiment Station in the School of Pharmacy at the University of Wisconsin–Madison. Sacchetti Tr. 1162:19-1163:24; DDX-ZYDUS-3.2; DTX-ZYDUS-1, Curriculum Vitae of Dr. Mark Sacchetti. Dr. Sacchetti was recognized without objection as an expert in solid state chemistry, pharmaceutical science, polymorphism and polymorph screening. Sacchetti Tr. 1166:4-10.

5. The Asserted Claims and the '283 Patent

1704. Asserted claims 2 and 27, and the claims from which they depend, read:

1. An unsolvated crystal form of the compound of Formula (I):



which is enantiomerically pure, wherein the crystal form is Form A, which has an X-ray powder diffraction pattern comprising peaks at about 8.1, 14.4, 17.4, 23.6 and 25.1 degrees 2θ, or Form F, which has an X-ray powder diffraction pattern comprising peaks at about 8.1, 15.6, 17.3, and 25.4 degrees 2θ.

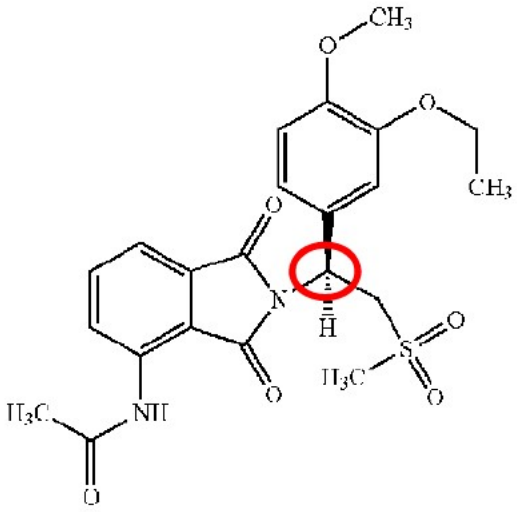
2. The crystal form of claim 1, wherein the crystal form is Form A, which has an X-ray powder diffraction pattern comprising peaks at about 8.1, 14.4, 17.4, 23.6 and 25.1 degrees 2θ.

27. A solid pharmaceutical composition comprising the crystal form of claim 2.

Sacchetti Tr. 1171:11-23; JTX-6.66 (59:20-49, 60:59-60), U.S. Patent No. 8,093,283 ("'283 patent"). The five peaks listed in claim 2 are inherent properties of crystalline apremilast Form A. Sacchetti Tr. 1171:24-1172:1; Myerson Tr. 1616:25-1617:5.

6. Claim Construction

1705. Claim 1 includes the term "enantiomerically pure." Court has construed "enantiomerically pure" as "a stereomerically pure composition of a compound having one chiral center." Stereomerically pure is defined as "a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound." Apremilast has one chiral center (circled below). The '283 patent pertains to enantiomerically pure apremilast. Sacchetti Tr. 1173:1-1174:7; DDX-ZYDUS-3.14; ECF No. 187, Agreed-to Claim Constructions; JTX-6.66 (59:20-40) ('283 patent).



B. Claims 2 and 27 of the '283 Patent are Anticipated by the '052 Publication.

1706. Claims 2 and 27 of the '283 patent are anticipated by the '052 publication. Sacchetti Tr. 1184:19-1188:17, 1191:19-22; DDX-ZYDUS-3.29-31, 38; DTX-179 ('052 publication).

1. The '052 Publication Discloses all Claim Limitations.

1707. The '052 publication teaches a method of making enantiomerically pure apremilast in Example 2: recrystallization from a solution of 2:1 ethanol/acetone. Sacchetti Tr. 1175:23-1176:5; DDX-ZYDUS-3.19; DTX-179.15 ([96]-[103]), U.S. Patent Application Publication No. 2003/0187052 A1 ("'052 publication"). Example 2 as presented in the '052 publication is identical to Example 2 in the '283 patent. Sacchetti Tr. 1175:23-1176:5, 1184:19-1185:8; DDX-ZYDUS-3.19; DTX-179.15 ([96]-[103]) ('052 publication); JTX-6.56 (39:17-40:46) ('283 patent).

'283 Patent: Example 2	**'052 Publication: Example 2**
Preparation of Compound A A 500 mL 3-necked round bottom flask was equipped with a mechanical stirrer, thermometer, and condenser. The reaction vessel was charged with (S)-2-(3-ethoxy-4-methoxyphenyl)-1-(methylsulphonyl)-eth-2-	Preparation of Compound A A 500 mL 3-necked round bottom flask was equipped with a mechanical stirrer, thermometer, and condenser. The reaction vessel was charged with (S)-2-(3-ethoxy-4-methoxyphenyl)-1-(methylsulphonyl)-eth-2-

yl amine N-acetyl-L-leucine salt (25 g, 56 mmol, 98% ee), 3-acetamidophthalic anhydride (12.1 g, 58.8 mmol), and glacial acetic acid (250 mL). The mixture was refluxed over night and then cooled to <50° C. The solvent was removed in vacuo, and the residue was dissolved in ethyl acetate. The resulting solution was washed with water (250 mL×2), saturated aqueous NaHCO3 (250 mL×2), brine (250 mL×2), and dried over sodium sulphate. The solvent was evaporated in vacuo, and the residue recrystallized from a binary solvent containing ethanol (150 mL) and acetone (75 mL). The solid was isolated by vacuum filtration and washed with ethanol (100 mL×2). The product was dried in vacuo at 60° C. to a constant weight, affording 19.4 g (75% yield) of S-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetamidoisoindoline-1,3-dione} with 98% ee. Chiral HPLC (15/85 EtOH/20 mM KH2PO4 @ pH 5, Ultron Chiral ES-OVS from Agilent Technology, 150 mm×4.6 mm, 0.4 mL/min, @ 240 nm): 25.4 min (S-isomer, 98.7%), 29.5 min (R-isomer, 1.2%). 1H-NMR (CDCl3) δ: 1.47 (t, 3H), 2.26 (s, 3H), 2.87 (s, 3H), 3.68-3.75 (dd, 1H), 3.85 (s, 3H), 4.07-4.15 (q, 2H), 4.51-4.61 (dd, 1H), 5.84-5.90 (dd, 1H), 6.82-8.77 (m, 6H), 9.46 (s, 1H); 13C-NMR (DMSO-d6) δ: 14.66, 24.92, 41.61, 48.53, 54.46, 55.91, 64.51, 111.44, 112.40, 115.10, 118.20, 120.28, 124.94, 129.22, 131.02, 136.09, 137.60, 148.62, 149.74, 167.46, 169.14, 169.48.	yl amine N-acetyl-L-leucine salt (25 g, 56 mmol, 98% ee), 3-acetamidophthalic anhydride (12.1 g 58.8 mmol), and glacial acetic acid (250 mL). The mixture was refluxed over night and then cooled to <50° C. The solvent was removed in vacuo, and the residue was dissolved in ethyl acetate. The resulting solution was washed with water (250 mL×2), saturated aqeous NaHCO3 (250 mL×2), brine (250 mL×2), and dried over sodium sulphate. The solvent was evaporated in vacuo, and the residue recrystallized from a binary solvent containing ethanol (150 mL) and acetone (75 mL). The solid was isolated by vacuum filtration and washed with ethanol (100 mL×2). The product was dried in vacuo at 60° C. to a constant weight, affording 19.4 g (75% yield) of S-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-[acetyl]aminoisoindoline-1,3-dione with 98% ee. Chiral HPLC (15/85 EtOH/20 mM KH2PO4 @ pH 3.5, Ultron Chiral ES-OVS from Agilent Technology, 150 mm×4.6 mm, 0.4 mL/min., @ 240 nm): 25.4 min (S-isomer, 98.7%), 29.5 min (R-isomer, 1.2%). 1H-NMR (CDCl3) δ:1.47 (t, 3H), 2.26 (s, 3H), 2.87 (s, 3H), 3.68-3.75 (dd, 1H), 3.85 (s, 3H), 4.07-4.15 (q, 2H), 4.51-4.61 (dd, 1H), 5.84-5.90 (dd, 1H), 6.82-8.77 (m, 6H), 9.46 (s, 1H). 13C-NMR (DMSO-d6) δ: 14.66, 24.92,41.61, 48.53, 54.46, 55.91, 64.51, 111.44, 112.40, 115.10, 118.20, 120.28, 124.94, 129.22, 131.02, 136.09, 137.60, 148.62, 149.74, 167.46, 169.14, 169.48.

Sacchetti Tr. 1175:23-1176:5; DDX-ZYDUS-3.20; DTX-179.15 ([102]-[103]) ('052 publication); JTX-6.56 (40:15-44) ('283 patent).

1708. The '052 publication provides for recrystallization of enantiomerically pure apremilast from 2:1 mixture of ethanol and acetone. Sacchetti Tr. 1184:19-1185:8; DDX-ZYDUS-3.29; DTX-179.15 ([96]-[103]) ('052 publication). A POSA would understand this

process to be a typical recrystallization: (1) stir solution at reflux for sufficient time to dissolve the compound; (2) filter; and (3) cool to room temperature by removing from heat and possibly immerse in an ice/water bath (as described in the Fieser reference). Sacchetti Tr. 1184:19-1185:8; DDX-ZYDUS-3.29; DTX-179.15 ([96]-[103]) ('052 publication). A POSA would describe this recrystallization as consistent with "fast cooling." Sacchetti Tr. 1185:9-13; DDX-ZYDUS-3.29; DTX-179.15 ([96]-[103]) ('052 publication). This results in chemically purified apremilast that would inherently be Form A. Sacchetti Tr. 1185:14-16; DDX-ZYDUS-3.29; DTX-179.15 ([96]-[103]) ('052 publication).

1709. The '283 patent describes only one specific method for making crystalline apremilast Form A: crystallizing apremilast from ethanol, acetone, or a mixture thereof by fast cooling. Sacchetti Tr. 1176:1-1177:13, 1185:19-1186:16; Myerson Tr. 1617:11-14; DDX-ZYDUS-3.29; JTX-6.56 (39:17-40:46) ('283 patent). Example 2 in the '052 publication, as practiced by a POSA, would inevitably yield Form A as a result of fast cooling from a mixture of ethanol and acetone. Sacchetti Tr. 1185:19-1186:16; DDX-ZYDUS-3.30; DTX-179.1 (Abstract), 15 ([96]-[103]) ('052 publication); JTX-6.4, 40 (7:30-31), 56 (39:17-40:46) ('283 patent). A POSA would have taken the inventors of the '283 at their word (given under oath) and would have understood that they knew how to make crystalline apremilast Form A and disclosed how to make Form A in the '283 patent. Sacchetti Tr. 1186:17-24; PTX-865.125-26, Certified File History for U.S. Patent No. 8,093,283.

1710. The '283 patent discloses a single method of obtaining enantiomerically pure crystalline apremilast: Example 2. Sacchetti Tr. 1172:5-20; DDX-ZYDUS-3.11; JTX-6.56 (40:15-46) ('283 patent).

1711. The inventors of the ’283 patent disclosed in the patent specification a single method of making crystalline apremilast Form A. Sacchetti Tr. 1172:24-1173:6; JTX-6.45 (18:32-38) (’283 patent). This process employs a recrystallization from acetone, ethanol, and mixtures thereof using fast cooling. Sacchetti Tr. 1172:24-1173:6; JTX-6.45 (18:32-38) (’283 patent). Fast cooling involves allowing the solution to cool naturally to room temperature or lower. Sacchetti Tr. 1173:10-17. The ’283 patent specifies that crystallization by fast cooling is a distinctive embodiment to make Form A. Sacchetti Tr. 1173:7-9; DDX-ZYDUS-3.12; JTX-6.45 (18:32-38) (’283 patent).

1712. Claim 2 of the ’283 patent is anticipated because Example 2 of the ’052 publication inherently discloses crystalline apremilast Form A, and the XRPD pattern and 5 peaks listed in claim 2 are inherent properties of Form A. Sacchetti Tr. 1185:19-1186:16; DDX-ZYDUS-3.30; DTX-179.1 (Abstract), 15 ([96]-[103]) (’052 publication); JTX-6.4, 40 (7:30-31), 56 (39:17-40:46) (’283 patent). Dr. Steed agrees with Dr. Sacchetti that Example 2 of the ’052 publication inherently discloses crystalline apremilast Form A, and the XRPD pattern and 5 peaks listed in claim 2 are inherent properties of Form A. Steed Tr 1105:10-22; 1138:7-10.

1713. The ’052 publication and ’283 patent provide identical descriptions and examples of pharmaceutical compositions comprising enantiomerically pure apremilast. Sacchetti Tr. 1176:6-10, 1185:19-1186:16; DDX-ZYDUS-3.30; DTX-179.1 (Abstract), 15 ([96]-[103]) (’052 publication); JTX-6.4, 40 (7:30-31), 56 (39:17-40:46) (’283 patent). The ’052 publication teaches the utility of apremilast for treatment of various diseases including psoriasis. Sacchetti Tr. 1176:11-14; DDX-ZYDUS-3.19; DTX-179.1 (Abstract) (’052 publication).

1714. Claim 27 of the ’283 patent is anticipated because the ’052 publication inherently discloses Form A and teaches pharmaceutical compositions of enantiomerically pure apremilast

comprising Form A. Sacchetti Tr. 1176:6-10; DDX-ZYDUS-3.30; DTX-179.1 (Abstract), 15 ([96]-[103]) ('052 publication); JTX-6.4, 40 (7:30-31), 56 (39:17-40:46) ('283 patent).

2. Dr. Myerson Does Not Argue the Asserted Claims Are Not Enabled.

1715. The '283 patent describes only one specific method for making crystalline apremilast Form A: crystallizing apremilast from ethanol, acetone, or a mixture thereof by fast cooling. Sacchetti Tr. 1176:1-1177:13, 1185:19-1186:16; Myerson Tr. 1617:11-14; DDX-ZYDUS-3.29; JTX-6.56 (39:17-40:46) ('283 patent).

1716. At trial, Dr. Myerson offered no opinion that the '283 patent specification does not contain sufficient written description for a POSA to be able to make crystalline apremilast Form A or that the asserted claims are not enabled. Myerson Tr. 1614:5-8. Nor does Dr. Myerson contend that the Celgene inventors were dishonest or falsified information to the patent office. Myerson Tr. 1615 13-16. Dr. Myerson further acknowledges that the '283 patent specification does not exclude any ratio of acetone to ethanol from its description of how to make crystalline apremilast Form A, a description he acknowledge is sufficient. Myerson Tr. 1615:5-12.

3. Third-Party Experiments Do Not Contradict Anticipation.

1717. Parties in opposition to European counterpart of the '283 patent offered experiments that appear to show that Example 2 results in apremilast Form B when using fast cooling. Myerson Tr. 1579:2-1583:24; Sacchetti Tr. 1187:10-20; DDX-ZYDUS-3.31. This stands in direct contrast to the disclosures of the '283 patent, which state that Example 2 using fast cooling results in Form A. Sacchetti Tr. 1187:10-20. The opponents to the European counterpart include parties that use Form B and thus their laboratories could have been seeded with Form B crystals. Sacchetti Tr. 1187:21-1188:17; DDX-ZYDUS-3.31. There is no evidence that the opponents followed good laboratory practice to ensure there was no inadvertent seeding.

Sacchetti Tr. 1187:21-1188:17; DDX-ZYDUS-3.31. Specifically, there is no evidence of filtering solutions to remove seeds before cooling and no evidence of refluxing for sufficiently long time to dissolve seeds. Sacchetti Tr. 1187:21-1188:17; DDX-ZYDUS-3.31.

1718. Alternatively, in defending its patent from the third-party oppositions, Celgene submitting evidence of testing that Celgene represented was faithful to Example 2 but purportedly resulted in crystalline apremilast Form C. Steed Tr. 1108:1-8.

1719. At trial, Dr. Myerson acknowledged that he made no investigation to determine whether the laboratories of the opponents may have been contaminated with Form B, whether the opponents were in the business of making or using Form B, whether the experiments included hot filtration, or whether the solutions were refluxed for a significant period of time. Myerson Tr. 1620:11-1623:20.

C. Claims 2 and 27 of the '283 Patent Are Obvious Over the '052 Publication In View of Fieser, Guillory, and Byrn 1994 and Knowledge of a POSA.

1720. Claims 2 and 27 of the '283 patent are obvious over the '052 publication in view of Fieser, Guillory, and Byrn 1994 as well as the general knowledge of a POSA. Sacchetti Tr. 1188:23-1191:13, 1191:19-24; DDX-ZYDUS-3.33-36, 38; DTX-101 (Byrn 1994); DTX-125 (Guillory); DTX-179 ('052 publication); JTX-6 ('283 patent); JTX-178 (Fieser).

1. Person Of Ordinary Skill in The Art For The '283 Patent.

1721. A POSA with respect to the claimed subject matter would include a person who possesses an advanced degree (e.g., Master's degree or Ph.D., or foreign equivalents of either of the foregoing) in the fields of solid state chemistry or a related discipline, such as physical chemistry or pharmaceutical science, and several years of experience in the pertinent field. A POSA could have a lower level of formal education, such as a Bachelor's degree, if such a

person had more years of experience in the field of pharmaceutical science or solid state chemistry. Sacchetti Tr. 1174:13-21; DDX-ZYDUS-3.16.

1722. A POSA would have worked as part of a team that included one or more other people of ordinary skill in the art with respect to one or more other aspects of the claims of the patents. The other people of ordinary skill in the art would have expertise and knowledge obtained through his or her educational, industrial, or academic experiences, including specialties in medicinal chemistry, organic or synthetic chemistry, pharmaceutical formulation, pharmacology, medicine, and clinical use. Sacchetti Tr. 1174:25-1175:7; DDX-ZYDUS-3.16.

1723. The '283 is invalid for obviousness whether the Court adopts Dr. Sacchetti's or Dr. Myerson's definition of a POSA. Sacchetti Tr. 1175:11-14.

2. The Scope and Content of the Prior Art.

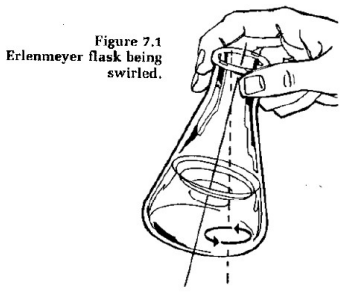
a. The '052 Publication

1724. For a discussion of the relevant disclosures of the '052 publication, *see* above ¶¶ 1707-1714.

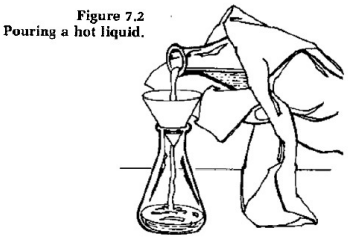
b. Fieser

1725. Fieser is a textbook for sophomore organic chemistry laboratory courses. Sacchetti Tr. 1177:16-1178:1; DDX-ZYDUS-3.21; JTX-178, Louis F. Fieser & Kenneth L. Williamson, *Crystallization*, *in* ORGANIC EXPERIMENTS (3rd ed. 1975) ("Fieser"). Fieser teaches that recrystallization is a "highly effective method of purifying a solid substance." Sacchetti Tr. 1177:16-1178:1; DDX-ZYDUS-3.21; JTX-178.5-8 (Fieser). Fieser describes methods to crystallize a compound including: (1) cooling a solution to produce supersaturation; and (2) solvent/antisolvent pairs. A compound may not crystallize readily from a single solvent. Sacchetti Tr. 1177:16-1178:1; DDX-ZYDUS-3.21; JTX-178.5-8 (Fieser).

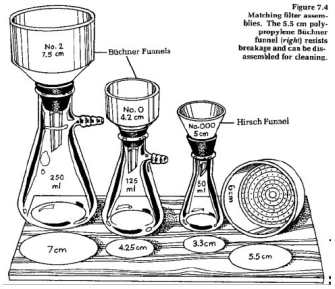
1726. Fieser discloses that recrystallization is "[a] highly effective method of purifying a solid substance consists in [sic] dissolving it in a suitable solvent at the boiling point, filtering the hot solution by gravity to remove any suspended insoluble particles, and letting crystallization proceed." Sacchetti Tr. 1178:4-17; DDX-ZYDUS-3.22; JTX-178.5, 8 (Fieser). The solution is then left to "stand undisturbed at room temperature until the solution has acquired the temperature of the surroundings and crystals have ceased to increase in number or size; the flask is then chilled in an ice bath to promote further crystallization. The crystals that have separated in this first crop are collected by suction filtration and washed free of mother liquor with a little fresh, chilled solvent." Sacchetti Tr. 1178:21-1179:9; DDX-ZYDUS-3.23; JTX-178.5, 10 (Fieser). The images from Fieser depicted below illustrate the simplicity of this process, of which a college sophomore of ordinary skill in the art would have been capable. Sacchetti Tr. 1178:21-1179:9; DDX-ZYDUS-3.22-23; JTX-178.5, 10 (Fieser).



1. Dissolving the compound



2. Filtering the hot solution



3. Filtering the crystallized solid

c. Byrn 1994

1727. Byrn 1994 describes a variety of factors that influence polymorphic form obtained during crystallization or recrystallization: (1) solvent composition or polarity; (2) concentration or degree of supersaturation; (3) temperature, including cooling rate and the cooling profile; (4) intentional and inadvertent seeding; (5) pH; (6) additives; and (7) agitation. Sacchetti Tr. 1179:13-1180:13; DDX-ZYDUS-3.24; DTX-101.3, S.R. Byrn et al., *Solid-State Pharmaceutical*

Chemistry, 6 CHEM. MATER. 1148 (1994) ("Byrn 1994"). "Seeding comes in two categories. There's so-called intentional seeding and then inadvertent seeding. . . . [I]ntentional seeding occurs when a POSA adds seeds of a particular polymorph during the supersaturation step to help nucleate and crystallize that particular polymorph. Inadvertent seeding occurs, as the name implies, when seeds are not added, but they're present nonetheless. And their presence can result in crystallization of that particular inadvertent seeded form." Sacchetti Tr. 1180:2-13; DDX-ZYDUS-3.24; DTX-101.3 (Byrn 1994). Inadvertent seeding issues arise "because thermodynamically more stable forms are less soluble and can require a longer period of time to dissolve the seeds." Sacchetti Tr. 1180:14-1181:11. Preventing inadvertent seeding requires precautionary measures, including heating the solution for a sufficient amount of time to dissolve seeds and/or filtering to remove seeds. Sacchetti Tr. 1180:14-1181:11. Polymorphs can be uniquely identified by their X-ray powder diffraction pattern. Sacchetti Tr. 1181:12-16; DDX-ZYDUS-3.24; DTX-101.3, 6 (Byrn 1994).

d. Guillory

1728. Guillory teaches the necessity of conducting polymorph screens during pharmaceutical development. Sacchetti Tr. 1181:19-1182:15; DDX-ZYDUS-3.25; DTX-125.5-23 (Guillory). During regulatory registration there is a need to ascertain whether other solid forms will appear during purification, processing, and production. Sacchetti Tr. 1181:19-1182:15; DDX-ZYDUS-3.25; DTX-125.5-23 (Guillory). Guillory teaches the need to ensure polymorphic form is consistent to prevent problems that could adversely affect manufacturing, safety, and efficacy. Sacchetti Tr. 1181:19-1182:15; DDX-ZYDUS-3.25; DTX-125.5-23 (Guillory).

1729. Guillory describes a number of screening methods useful in the identification of polymorphs: (1) crystallization from solvents; (2) slurrying/equilibration; (3) thermal treatment;

(4) grinding; and (5) other methods. Sacchetti Tr. 1181:19-1182:15; DDX-ZYDUS-3.25; DTX-125.5-23 (Guillory).

1730. Regarding crystallization from solvents, Guillory describes that supersaturation can be achieved by: (1) fast cooling; (2) slow cooling; (3) evaporation; and (4) solvent/antisolvent pairs. Sacchetti Tr. 1182:18-1183:1; DDX-ZYDUS-3.26; DTX-125.9-10 (Guillory). Guillory teaches that solvents selected for polymorph screening should include any solvent that the compound comes into contact with during synthesis, purification, and processing. Sacchetti Tr. 1183:12-22; DDX-ZYDUS-3.26; DTX-125.9 (Guillory). Table 1 in Guillory (below) provides list of common solvents including water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, and hexane. Sacchetti Tr. 1183:25-1184:11; DDX-ZYDUS-3.26; DTX-125. 10 (Guillory). POSAs would have been familiar with these commonly used solvents and would have been motivated to include them in polymorph screening. Sacchetti Tr. 1183:25-1184:11; DDX-ZYDUS-3.27; DTX-125.10 (Guillory)..

Table 1 Solvents Often Used in the Preparation of Polymorphs

Solvent	Boiling point (°C)
Dimethylformamide	153
Acetic acid	118
Water	100
1-Propanol	97
2-Propanol	83
Acetonitrile	82
2-Butanone	80
Ethyl acetate	77
Ethanol	78
Isopropyl ether	68
Hexane	69
Methanol	65
Acetone	57
Methylene chloride	40
Diethyl ether	35

3. The Prior Art Discloses All Claim Limitations.

1731. The ’283 patent describes only one specific method for making crystalline apremilast Form A, namely, crystallization from ethanol, acetone, or a mixture thereof by fast cooling. Sacchetti Tr. 1188:23-1189:18; DDX-ZYDUS-3.33; JTX-6.56 (39:17-40:46) (’283 patent). Fieser, Guillory, and Byrn 1994 teach methods for crystallizing or recrystallizing from a single solvent or a mixture of solvents. Sacchetti Tr. 1188:23-1189:18; DDX-ZYDUS-3.33; DTX-101.3-6 (Byrn 1994); DTX-125.9-16 (Guillory); JTX-178.5-9, (Fieser). For example, Fieser describes recrystallization by fast cooling: (1) dissolve compound at the boiling point; (2) filter the solution, and (3) cool to room temperature or lower. Sacchetti Tr 1188:23-1189:18; DDX-ZYDUS-3.33; JTX-178.5-9, (Fieser).

1732. Example 2 of the ’052 publication teaches the recrystallization of stereomerically pure apremilast from 2:1 ethanol/acetone but does not state the cooling rate used in the experiment. Sacchetti Tr. 1189:21-1190:12; DDX-ZYDUS-3.34; DTX-179.15 ([96]-[103]) (’052 publication). Guillory and Byrn 1994 teach that varying cooling rates can result in different polymorphs. DTX-101.3 (Byrn 1994); DTX-125.9-11 (Guillory). For example, Guillory describes: (1) slow cooling by controlled temperature change; and (2) quench cooling using an ice/water bath. DTX-125.10 (Guillory).

1733. Based on teachings of Fieser, Guillory, and Byrn 1994, a POSA would have been motivated to try at least fast and slow cooling rates in the procedure set forth in Example 2 of the ’052 publication, and would have reasonably expected to succeed in producing enantiomerically pure apremilast in crystalline form. Sacchetti Tr. 1190:16-1191:2; DDX-ZYDUS-3.35; DTX-101.3 (Byrn 1994); DTX-125.9-11 (Guillory); JTX-6.56 (39:17-40:46) (’283 patent); JTX-178.5-15 (Fieser); DTX-179.15 ([96]-[103]) (’052 publication). Fast cooling would inherently produce apremilast Form A crystals exhibiting the five peaks in claim 2 of the ’283 patent when analyzed

by XRPD. Sacchetti Tr. 1190:16-1191:2; DDX-ZYDUS-3.35; DTX-101.3 (Byrn 1994); DTX-125.9-11 (Guillory); JTX-6.56 (39:17-40:46) ('283 patent); JTX-178.5-15 (Fieser).

1734. Based on teachings about the therapeutic utility of apremilast in the '052 publication, a POSA would have been motivated to formulate the enantiomerically pure apremilast Form A obtained from Example 2 into pharmaceutical compositions, and would have reasonably expected to succeed in those efforts, so claim 27 is obvious. Sacchetti Tr. 1191:5-13; DDX-ZYDUS-3.36; DTX-179.7-8 ([36]-[45], [49]) ('052 publication).

4. Dr. Myerson Agrees That the Asserted Claims Are Obvious.

1735. A POSA would have been motivated to conduct a polymorph screen based on the disclosures of the '052 publication. Myerson Tr. 1630:3-13.

1736. Dr. Myerson agrees that fast cooling from a solvent containing ethanol and actetone leads to crystalline apremilast Form A. Myerson Tr. 1614:9-13. Dr. Myerson agrees that performing this process using other ratios of ethanol to acetone leads to Form A, and is "sure there are other ways to make Form A." Myerson Tr. 1614:14-23.

1737. Dr. Myerson admitted at trial that Example 2 of the '283 patent discloses a polymorph screen. Myerson Tr. 1617:22-24. Dr. Myerson further admitted that Guillory would have taught a POSA "lots of techniques" to use in a polymorph screen and that a POSA could have designed a polymorph screen based on the teachings of Guillory. Myerson Tr. 1626:24-1627:8. Dr. Myerson agrees that ethanol and acetone are on the list of typical polymorph screen solvents disclosed in Guillory. Myerson Tr. 1627:12-15. Dr. Myerson further agrees that Guillory teaches the use of fast cooling. Myerson Tr. 1627:18-22. Dr. Myerson testified that Guillory teaches that a polymorph screen should include solvents encountered during formulation and processing, which for the '052 publication would include ethanol, acetone, and mixtures thereof. Myerson Tr. 1628:3-11.

1738. Dr. Myerson stated at trial that he agrees that the preclinical tests in the '052 patent would have provided motivation to a POSA to conduct a polymorph screen on enantiomerically pure apremilast. Myerson Tr. 1629:2-1630:13. Dr. Myerson acknowledged that the only example for making enantiomerically pure apremilast in the '052 patent is Example 2. Myerson Tr. 1630:14-18. Dr. Myerson further agrees that Example 2 teaches the use of a mixture of ethanol and acetone in the final recrystallization step. Myerson Tr. 1630:24-1631:3. Dr. Myerson admitted that a POSA would have been motivated to do a polymorph screen on enantiomerically pure apremilast using ethanol, acetone, and mixtures thereof. Myerson Tr. 1631:4-10. Dr. Myerson agrees that a POSA would have been motivated to carry out the recrystallization of Example 2 using fast cooling. Myerson Tr. 1631:14-19, 1633:6-10. Dr. Myerson, summarizing, stated at trial that a POSA would have been able to design a polymorph screen using ethanol, acetone, and mixtures thereof, and varying cooling rates, including fast cooling. Myerson Tr. 1631:20-25. At trial, on impeachment, Dr. Myerson agreed with his deposition testimony wherein he stated that "there must be some parameters with respect to acetone, ethanol, and mixtures thereof, and fast cooling that must result in Form A . . . ." Myerson Tr. 1632:6-1633:5. Dr. Myerson agreed that a POSA would have reasonably expected to succeed in recrystallizations based on Example 2 and that a POSA would have been able to determine the diffraction peaks of the resulting crystalline material. Myerson Tr. 1633:11-18.

1739. Thus, Dr. Myerson agrees with Dr. Sacchetti that the '052 publication, in combination with Fieser, Guillory, and Byrn 1994 would have led a POSA to conduct a polymorph screen that would have resulted in crystalline apremilast Form A with a reasonable expectation of success. Myerson Tr. 1614:9-1633:18; Sacchetti Tr. 1188:23-1191:13.

5. Amgen Has Advanced No Objective Indicia.

1740. At trial, Amgen advanced no evidence of objective indicia of nonobviousness with respect to the '283 patent. Myerson Tr. 1571:23-1635:7.

X. The Asserted Claims Of The '541 Patent Are Invalid.

A. The Person Of Ordinary Skill In The Art For The '541 Patent.

1800. As of August 15, 2014, a POSA with respect to the '541 patent would have been a physician specializing in dermatology or rheumatology, having an M.D., or a Ph.D. in pharmacology, biochemistry, or related discipline and significant clinical experience in one or both of these medical sub-specialties. Gilmore Tr. 831:5-14. A POSA would have had access to and consulted with a multidisciplinary team of ordinarily skilled artisans in related and relevant disciplines such as pharmacology and chemistry. *Id.*

1801. Amgen has not offered a POSA definition that is materially different. Alexis Tr. 1751:21-1752:17.

B. Scope And Content Of The Prior Art For The '541 Patent.

1802. The '536 patent issued on June 4, 2013, before the August 15, 2014 effective filing date for the '541 patent. JTX-7.2; Gilmore Tr. 832:7-9, 21-22. Although the '536 patent issued in 2013, the disclosures in the '536 patent are based on research that was performed in the early 2000s. Gilmore Tr. 832:23-833:1; Alexis Tr. 1815:3-17 (agreeing that the information within the '536 patent was in existence as of March 20, 2002).

1803. The '536 patent is generally related to methods of using apremilast in the treatment of certain diseases, and compositions comprising the same. JTX-7.6 (1:14-16); Gilmore Tr. 833:8-11. The '536 patent discloses that suitable dosing regimens for apremilast "can be readily selected by those skilled in the art." JTX-7.12 (13:47-49). In particular, the '536 patent teaches that apremilast therapy "should be initiated at a lower dose, perhaps about 1 mg to

about 25 mg, and increased if necessary up to about 200 mg to about 1000 mg per day as either a single dose or divided doses." JTX-7.12 (13:59-63); Gilmore Tr. 833:12-20.

1804. Claim 1 of the '536 patent teaches a POSA a method of treating psoriasis using stereomerically pure apremilast in dose ranges of about 10 mg to 200 mg per day in tablet or capsule form as either a single dose or a divided dose. JTX-7.20-21 (claim 1); Gilmore Tr. 833:21-834:1; Alexis Tr. 1816:11-13. A POSA would have understood that claim 1 is teaching 10 mg as the lowest starting dose of apremilast for the treatment of psoriasis. Gilmore Tr. 834:2-5.

1805. The '536 patent does not specifically teach which doses of apremilast are safe and effective for administration to patients with psoriasis. Gilmore Tr. 834:6-9. Nor is there any clinical data presented in the '536 patent relating to the treatment of psoriasis with apremilast. Gilmore Tr. 834:10-12, 946:18-20; Alexis Tr. 1802:20-23 (testifying that he does not recall seeing any clinical data in the '536 patent regarding the administration of apremilast to humans), 1816:18-25 (agreeing that he "did not point to any human data related to this broad range of doses" in the '536 patent).

1806. After the '536 patent was disclosed in 2002, further information became available in the prior art, i.e., Papp 2012 and Schett 2012, relating to clinically safe and effective doses of apremilast for administration to psoriasis patients, as well as titrating the dose of apremilast to mitigate side effects. Gilmore Tr. 834:13-17, 946:21-947:2; Alexis Tr. 1816:18-1817:15 (agreeing that human data regarding the dosing of apremilast was available in Pap 2012 and Schett 2012, which he relied on during his direct testimony). A POSA would have considered Papp 2012 to be more informative regarding the appropriate dosing and dose titration of apremilast because it contains clinical data on efficacy for the treatment of psoriasis as well as

adverse events associated with apremilast treatment. Gilmore Tr. 947:3-13; Alexis Tr. 1803:2-6 (agreeing that as a clinician, he would be interested in seeing data regarding the administration of apremilast to humans with psoriasis before offering a dose to patients). As Amgen's expert Dr. Alexis recognizes, Papp 2012 was published in "a very prestigious journal," one that is a "leading international journal based in the U.K. for all branches of medicine." Alexis Tr. 1781:5-15, 1826:1-4. As such, Papp 2012 "would be a very credible source of information." Alexis Tr. 1781:21-1782:8, 1826:5-8 (admitting that a POSA looking at Papp 2012 would think that it is "credible evidence, scientific evidence").

1807. Papp 2012 is an article titled "Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial" published online in *The Lancet* on June 29, 2012, before the August 15, 2014 effective filing date of the '541 patent. DTX-153.1; Gilmore Tr. 832:7-9, 835:4-6. As such, Papp 2012 is prior art to the '541 patent. Alexis Tr. 1825:19-21. The named inventor of the '541 patent, Robert Day, is listed as one of the authors of Papp 2012. Alexis Tr. 1825:22-25. Papp 2012 reports the results from a phase 2b multicenter, randomized, placebo-controlled, dose-ranging clinical trial investigating the "clinical efficacy and safety of different doses of apremilast in the treatment of patients with moderate to severe plaque psoriasis." DTX-153.1; Gilmore Tr. 835:7-9, 835:21-24; Alexis Tr. 1826:16-1827:7. The doses of apremilast being investigated in Papp 2012 were 10 mg, 20 mg, and 30 mg twice daily. Gilmore Tr. 838:10-839:4; Alexis Tr. 1827:8-10; DTX-153.1. Celgene Corporation funded the clinical study that is reported in Papp 2012. DTX-153.1; Gilmore Tr. 835:10-12.

1808. Papp 2012 provides that apremilast, "given orally at 20 mg or 30 mg twice daily, seems to be efficacious, safe, and tolerable for patients with moderate to severe plaque psoriasis." DTX-153.1; Gilmore Tr. 835:25-836:4. Papp 2012 further discloses that "[a]lthough

no statistical comparisons between apremilast doses were done, apremilast 30 mg had the most favourable outcome and this dose is being investigated for patients with moderate to severe plaque psoriasis in phase 3 trials." DTX-153.7; Gilmore Tr. 836:5-11, 836:15-21; Alexis Tr. 1827:15-1828:8 (admitting that Papp 2012 is telling a POSA that "Phase 3 trials are in development or underway and are looking at the 30-milligran twice a day dosage," which is the last phase of drug development), 1828:9-13 (testifying that all of the phase 3 trials for apremilast "involved 30 milligrams twice a day for psoriasis"). Dr. Alexis testified that he was not asked to opine regarding the obviousness of using 20 mg of apremilast twice a day versus 30 mg twice a day for treating patients with psoriasis. Alexis Tr. 1828:15-18.

1809. Papp 2012 also teaches that the patients in the study were assigned to one of four treatment groups: 10 mg twice daily, 20 mg twice daily, 30 mg twice daily, and placebo alone. DTX-153.2; Gilmore Tr. 838:19-839:4. The doses were "titrated in the first week to mitigate potential dose-dependent adverse events of apremilast; all patients reached the target dose by day 5." *Id.*; *see also* Alexis Tr. 1774:2-13 (testifying that Papp 2012 teaches dose titration "to mitigate potential dose dependent adverse events of apremilast, and that all patients arrived at their target dose by day 5, so within five days"), 1828:19-22. As Dr. Gilmore testified, a POSA would understand that the phrase "potential dose-dependent adverse events" to mean adverse events "which may be associated with administration of the medication in a dose-dependent manner." Gilmore Tr. 839:5-12. In other words, "as the dose increases, sometimes patients have more side effects." *Id.*; *see also* Alexis Tr. 1828:23-1829:4 (testifying that a dose-dependent adverse event means that ""there's a dose response relationship in the frequency or severity of adverse events; meaning that if the dose increases, the likelihood of an event would increase too"). As such, Papp 2012 teaches a POSA that "it would be of interest to try to mitigate those

side effects by slowly increasing the dose of the medication," otherwise known as dose titration. Gilmore Tr. 839:5-12; *see also* Alexis Tr. 1830:6-11(agreeing that Papp 2012 titrated the dose of apremilast upwards from a lower dose to a higher dose).

1810. Dr. Gilmore testified that a POSA would have readily understood what titration schedule was used in Papp 2012 based on the information provided in that study. Gilmore Tr. 839:13-17. In particular, a POSA would have understood from the Papp 2012 clinical trial that: (1) the doses of apremilast used were 10 mg, 20 mg, and 30 mg tablets; (2) patients were given two doses per day of the medication; and (3) patients reached the target dose of 30 mg twice daily on day 5. Gilmore Tr. 840:14-841:3, 841:9-14; Alexis Tr.1774:2-13, 1827:8-10.

1811. Based on these disclosures in Papp 2012, Dr. Gilmore testified that a POSA would assume that the "enrollees would have incremental symmetric or same magnitude increases in dose per day, or per period of time, until the maximum dose is achieved on day 5." Gilmore Tr. 839:18-840:3. A POSA would have known that the dose increases would be of the same magnitude because that is "the most simplistic explanation" and "oftentimes the way [physicians] titrate doses of medication." Gilmore Tr. 840:4-8. Accordingly, Dr. Gilmore outlined the "very logical step-wise fashion through which that dose would be increased during the first five days of therapy until the target dose could be reached on day 5" as follows:

	Papp 2012		
	1st Dose (mg)	**2nd Dose** (mg)	**Total dose** (per day)
Day 1	10	10	20
Day 2	10	10	20
Day 3	20	20	40
Day 4	20	20	40
Day 5	30	30	60
Day 6 (and thereafter)	30	30	60

Gilmore Tr. 840:14-841:3. There is no dispute that the above chart was the actual dosing titration schedule used in the clinical study underlying Papp 2012. Alexis Tr. 1835:21-25 (admitting that "this is the dosing schedule used in the clinical trial that Papp published in a manuscript in 2012 about in the Lancet"), 1836:9-18 (agreeing that on days 1-2 of the clinical trial protocol underlying Papp 2012, patients were administered 10 mg in the morning and 10 mg in the evening, for a total dose of 20 mg per day, on days 3-4 patients were administered 20 mg in the morning and 20 mg in the evening, for a total dose of 40 mg per day, and on day 5 patients were administered the maintenance dose of 30 mg twice a day, for a total dose of 60 mg per day). Dr. Alexis admitted this dosing titration schedule is a "predetermined and one-size-fits-all titration schedule that occurred over the span of five days." Alexis Tr. 1836:19-24.

1812. Thus, Papp 2012 discloses administering apremilast according to a fixed dosing titration schedule to mitigate gastro-intestinal related adverse events. Gilmore Tr. 841:15-20; Alexis Tr. 1832:11-25 (agreeing that the titration schedule ascribed to Papp 2012 is a one-size-fits-all dosing titration). According to Dr. Gilmore, it is "[h]ighly unlikely that any other type of dosing" schedule was used in Papp 2012 because a POSA would have expected the authors to "explain that or describe it in more detail," which they did not. Gilmore Tr. 841:21-842:2. In other words, the absence of detailed description of the titration schedule in Papp 2012 would have led a POSA to believe the most straightforward schedule was the one that was adopted and employed, i.e., a step-wise dose titration with equivalent dose increments and equivalent intervals between dose increases. Gilmore Tr. 842:5-8.

1813. Other prior art available as of the 2014 effective filing date further confirms the teachings of Papp 2012 regarding the dose titration schedule, in particular, the Pathan 2012 reference. Gilmore Tr. 842:9-17. Pathan is entitled, "Efficacy and safety of apremilast, an oral

phosphodiesterase 4 inhibitor, in ankylosing spondylitis." DTX-157.1; Gilmore Tr. 844:10-15. Pathan 2012 was published on September 14, 2012, and is another study funded by Celgene Corporation investigating the efficacy and safety of apremilast in treating ankylosing spondylitis, an inflammatory condition involving the bones and the spine. DTX-157.1; Gilmore Tr. 844:10-20, 845:4-14; Alexis Tr. 1839:1-8. Both Papp 2012 and Pathan 2012 were published in the same year, and thus Dr. Gilmore testified that it is likely the clinical trials were occurring around the same time. Gilmore Tr. 844:21-845:3.

1814. In Pathan 2012, the maximum maintenance dose was 30 mg twice daily, which was titrated over the first five days of treatment to optimize tolerability of the medication. DTX-157.2, 5; Gilmore Tr. 846:3-7; Alexis Tr. 1839:17-1840:6 (agreeing that the dose of apremilast being investigated in Pathan 2012 was 30 mg twice daily (or 60 mg per day)), 1844:1-4 (admitting that the dosing titration schedule used in Pathan 2012 for apremilast was designed to optimize tolerability). In particular, Pathan 2012 teaches that patients "were started on apremilast 10 mg twice daily or placebo and the dose was titrated by 20 mg every 2 days until the maximum dose of 30 mg twice daily was achieved on day 5," which is a fixed titration schedule. DTX-157.2; Gilmore Tr. 845:20-846:2; Alexis Tr. 1840:13-18, 1853:10-16 (testifying that Pathan 2012 "offers the most specificity as to what was done for the titration"). Dr. Gilmore testified that this is the exact same fixed dosing titration schedule for apremilast that was used in Papp 2012, and thus further confirms "the assumptions of what was written about the dose titration schedule in Papp 2012." Gilmore Tr. 846:25-847:15; Alexis Tr. 1842:22-1843:15 (admitting that Pathan 2012 "describes a dosing schedule consistent with the schedule" ascribed to Papp 2012). Although Pathan 2012 relates to a different disease state, a POSA reading Papp 2012 would have looked to Pathan 2012 because it is not "uncommon to use literature from

different fields," particularly when the literature is "talking about the same medication and understanding how to best deal with side effects associated with that medication." Gilmore Tr. 846:8-18; Alexis Tr. 1838:6-16 (admitting that prior art relating to other disease states (e.g., WO '102 for the treatment of sarcoidosis) can be relevant to the dosing titration of apremilast for psoriasis and psoriatic arthritis). According to Dr. Gilmore, "[t]hose types of issues are not dependent on the disease state." Gilmore Tr. 846:8-18

1815. In Papp 2012, at least 5% of patients still experienced treatment-emergent adverse events (e.g., headache, nausea, diarrhea) during the first 16 weeks of therapy, particularly in the initiation of treatment with apremilast. DTX-153.6; Gilmore Tr. 848:2-11. In particular, 18% of patients in the 30 mg BID treatment arm experienced nausea, 16% experienced upper respiratory tract infections, 14% experienced diarrhea, and 16% experienced tension headaches. DTX-153.5 (Table 2); Gilmore Tr. 848:12-23. Papp 2012 discloses that "[a]t least half these events occurred within the first 2 weeks of treatment and resolved within a week." DTX-153.6; Gilmore Tr. 848:2-11.

1816. Schett 2012 is an article titled "Oral Apremilast in the Treatment of Active Psoriatic Arthritis: Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled Study," published in *Arthritis & Rheumatism* in October 2012, before the August 15, 2014 effective filing date of the '541 patent. DTX-162.1; Gilmore Tr. 832:7-9, 849:18-850:1. Schett 2012 reports the results from a phase 2, multicenter, randomized, double-blind, placebo-controlled clinical study assessing "the efficacy and safety of apremilast, a novel orally available small molecule that specifically targets phosphodiesterase 4, in the treatment of active psoriatic arthritis (PsA)." DTX-162.1. The study indicates that patients with psoriatic arthritis were

treated with apremilast at a dose of 20 mg twice per day or 40 mg once per day. DTX-162.1; Gilmore Tr. 850:5-8.

1817. In Schett 2012, "[d]ose escalation was implemented during the first 7 days of treatment in an attempt to decrease the likelihood of adverse events (AEs) related to treatment initiation." DTX-162.2; Gilmore Tr. 850:16-20. The clinical trial described in Schett 2012 was registered with clinicaltrials.gov as NCT '092, which Schett 2012 incorporates by reference. DTX-162.1; Gilmore Tr. 850:21-25. As Dr. Gilmore testified, clinicaltrials.gov is a registration database run by the government for clinical trials performed in the United States. Gilmore Tr. 851:1-3; Gilmore Tr. 853:14-17. At the time Schett 2012 was published in October 2012, a POSA would have expected NCT '092 on clinicaltrials.gov to contain information regarding the study protocol, including how therapy is to be initiated, the dose administration, and the dose titration schedule. Gilmore Tr. 853:5-13, 853:18-854:6, 854:12-19. A POSA would have found it useful to look at the clinicaltrials.gov identifier disclosed in Schett 2012 to learn further information about the study. Gilmore Tr. 854:7-11. Dr. Gilmore testified that because there are generally page and word limits for scientific publications, and because it is generally more expensive to publish a longer article, it is not "an uncommon practice to have some information available online where it doesn't have to go into the printed article," such as in Schett 2012. Gilmore Tr. 854:20-855:6.

1818. The NCT '092 protocol discussed in Schett 2012, in turn, discloses a fixed dose titration of 10 mg once a day for days 1-3 followed by 20 mg once a day for days 4 to 7, during the first week of dosing to "ameliorate the dose dependent adverse events of [apremilast] (headache and GI disturbances)." DTX-92.3; Gilmore Tr. 857:9-14. As such, Schett 2012 and NCT '092 teach a POSA that a 10 mg once daily dose can be used as part of a dosing titration

schedule for apremilast. Gilmore Tr. 857:15-18. In Schett 2012, the maintenance dose was reached on day 8, which is the longest dosing titration schedule disclosed in the prior art for apremilast. Gilmore Tr. 863:15-19, 864:10-16.

C. The Asserted Claims Of The '541 Patent Are Obvious.

1. A POSA Would Have Been Motivated to Obtain Stereomerically Pure Apremilast with a Reasonable Expectation of Success.

1819. There is no dispute that the prior art as of 2014 discloses stereomerically pure apremilast, including stereomerically pure apremilast comprising greater than about 99% of the (+) isomer, and its use to treat patients with psoriasis, as required by claims 2, 19, and 21 of the '541 patent. *See* JTX-7.20-21 (claim 1); Gribble Tr. 617:16-618:6 (testifying that the stereomerically pure limitations in the '541 patent are rendered obvious by the prior art); Davies Tr. 1298:8-16 (testifying that he is only offering invalidity opinions regarding the '638 and '536 patents).

2. A POSA Would Have Been Motivated to Titrate the Dose of Apremilast in Increments of 10 mg Per Day Until Reaching a Maintenance Dose of 60 mg Per Day (or 30 mg Twice Per Day) on Day 6 to Mitigate Adverse Events.

1820. As discussed above, Papp 2012 teaches that 30 mg twice daily of apremilast had the most favorable outcome for treating patients with moderate to severe psoriasis, and that this dose was selected for further investigation in phase 3 clinical trials. DTX-153.7; Gilmore Tr. 836:15-24; Alexis Tr. 1827:15-1828:8. As such, a POSA reading these disclosures in Papp 2012 would have understood that the 30 mg twice a day (or BID) dose of apremilast was the most effective dose for treating psoriasis, showed the most promise, and was expected to be used as the maintenance dose in further studies. Gilmore Tr. 837:1-15; Alexis Tr. 1820:22-1821:8 (acknowledging that phase 3 clinical trials are designed to confirm the preliminary evidence accumulated in phase 2 studies regarding the safety and efficacy of a drug, and that phase 3 trials

are the last phase of the approval process), 1827:22-1828:2 (testifying that Papp 2012 tells a POSA that phase 3 trials are in development and "are looking at the 30-milligran twice a day dosage").

1821. A POSA would have known, as taught in Papp 2012 and Schett 2012, that although apremilast is generally well-tolerated, it is associated with certain dose-dependent, gastrointestinal-related adverse events, e.g., nausea and diarrhea. DTX-153.2; DTX-162.2; Gilmore Tr. 839:5-12; Alexis Tr. 1830:19-23 (testifying that "[i]t would have been known to a POSA that PDE4 inhibitors as a class," including apremilast, "has dose-dependent side effects"); Kim Tr. 1642:2-8 ("GI tolerability is one of the side effects associated with Otezla").

1822. As such, a POSA would have been motivated to titrate the dose of apremilast according to a fixed schedule during the first week of treatment, as taught in the prior art, to mitigate these dose-dependent adverse events. Gilmore Tr. 838:4-8, 838:19-839:12; DTX-153.2; Alexis Tr. 1830:16-18 (agreeing that a POSA would know from reading Papp 2012 that "dose titration can be used to mitigate adverse events"). Indeed, both as of 2014 and today, it is common and routine to titrate the dose of a drug that may be associated with treatment-related adverse events. Gilmore Tr. 838:9-15; Alexis Tr. 1754:6-15 (testifying that oral agents used for psoriasis as of 2014 were all medicines that "would undergo titration"). While Amgen and its expert, Dr. Alexis, claim that the multitude of drugs in the prior art that required dose titration were titrated according to the needs of the individual patient, i.e., were not titrated according to a fixed dosing schedule, Dr. Alexis admitted that none of these drugs were apremilast. Alexis Tr. 1813:23-25.

1823. Papp 2012 discloses that a significant number of patients in the 30 mg BID treatment arm still experienced treatment-related adverse events despite the 5-day dose titration,

e.g., nausea, diarrhea, and headaches, particularly during the first few weeks of treatment. DTX-153.5-6; Gilmore Tr. 847:20-848:23. For example, 18% of patients in the 30 mg BID treatment arm experienced nausea, 16% experienced upper respiratory tract infections, 14% experienced diarrhea, and 16% experienced tension headaches. DTX-153.5 (Table 2); Gilmore Tr. 848:12-23. Dr. Gilmore testified that these "percentage of adverse events, which are not pleasant type of adverse events, are quite significant and would indicate that there was room for optimization of the titration schedule, with the understanding that half of these events occur within the first two weeks of treatment." Gilmore Tr. 848:24-849:6. As such, a POSA would have been motivated to modestly extend the fixed dosing titration schedule in Papp 2012 to further improve the tolerability of apremilast in psoriasis patients. Gilmore Tr. 858:5-13.

1824. To adjust the dosing titration schedule in Papp 2012, a POSA would have been motivated to start at a lower dose of apremilast and decrease the magnitude of the dose increases to further ameliorate adverse events. Gilmore Tr. 858:5-13. The prior art taught starting apremilast at the lowest dose available, 10 mg per day, on day 1 instead of a 20 mg total dose on day 1. Gilmore Tr. 849:7-12. In particular, Schett 2012, incorporating by reference NCT '092, teaches the clinical administration of a 10 mg once a day dose as part of a titration schedule to mitigate gastrointestinal-related adverse events. DTX-162.1, 2; DTX-92.3; Gilmore Tr. 857:15-18. Other prior art references available as of 2014 further confirm that it would have been obvious to start with a 10 mg dose on day 1 and increase the dose in 10 mg increments. For example, claim 1 of the '536 patent teaches 10 mg as the lowest starting dose of apremilast for treating patients with psoriasis. Gilmore Tr. 834:2-5, 857:19-22; JTX-7.20-21 (claim 1). A POSA would have also understood from Papp 2012 that the lowest dose of apremilast that was clinically available in the prior art was 10 mg tablets. Gilmore Tr. 857:23-858:1.

1825. Thus, as Dr. Gilmore testified, a POSA would have been motivated to start with 10 mg of apremilast on the first day of treatment and increase the dose by 10 mg per day until reaching the target dose of 30 mg twice daily, or 60 mg per day, on day 6. Gilmore Tr. 858:18-859:3; DDX-4.33. Even assuming Papp 2012 does not disclose the specific dosing titration schedule used in that study, a POSA would have been motivated to titrate the dose of apremilast in the lowest dose that was clinically available, i.e., 10 mg, until reaching the maintenance dose on day 6, in light of the teachings of Papp 2012 that the dose of apremilast should be titrated during the first week to mitigate dose-dependent adverse events. Gilmore Tr. 838:19-839:12, 858:5-13, 858:18-859:3. This minor tweak to the Papp 2012 titration schedule results in the same dosing schedule claimed in claims 2, 19, and 21 of the '541 patent. Gilmore Tr. 859:19-22.

1826. A POSA would not have been motivated to extend the titration schedule in Papp 2012 by longer than a week. Gilmore Tr. 863:5-14. Dr. Gilmore testified that the gastrointestinal-related adverse events associated with apremilast "tend to be at the beginning of therapy," and that in the context of a clinical trial, patients need to get to the goal dose more quickly so that the investigators can start accumulating data on efficacy and safety. *Id.* As such, extending the titration schedule by a significant amount of time would not be a "realistic exercise," in light of the clinical data presented in Papp 2012. *Id.* In addition, there was nothing in the prior art that suggested extending the dose titration schedule for apremilast by longer than a week. Gilmore Tr. 864:10-16. Amgen's expert, Dr. Alexis, himself admitted that there was no literature or clinical data in the prior art providing a dosing titration schedule for apremilast extending beyond eight days. Alexis Tr. 1845:15-1846:6. The only publications in the prior art providing clinical data regarding the efficacy and safety of apremilast are Papp 2012, Schett 2012, and Pathan 2012, in which apremilast was dose-titrated to mitigate adverse events for a

period no longer than eight days. Alexis Tr. 1846:10-21. As discussed above, a POSA would have considered clinical data to be more informative regarding the appropriate dosing and dose titration of apremilast. Gilmore Tr. 947:6-13; Alexis Tr. 1803:2-6 (agreeing that as a clinician, he would be interested in seeing data regarding the administration of apremilast to humans with psoriasis before offering a dose to patients). Dr. Alexis acknowledged that he is not aware of any publications beyond Papp 2012, Schett 2012, and Pathan 2012 that describes the results of a clinical trial in which the dose of apremilast was titrated longer than eight days. Alexis Tr. 1846:22-1847:3.

1827. Further, despite what Amgen and its experts may argue, a POSA would not have been motivated to titrate apremilast to a maintenance dose higher than 30 mg twice daily or administer apremilast in multiples of 5 mg. Gilmore Tr. 923:7-924:4. Indeed, Dr. Alexis admitted that he has never given a patient 5 mg day, 100 mg a day, or 200 mg a day of apremilast, as disclosed in the '536 patent. Alexis Tr. 1817:16-25. Nor is Dr. Alexis aware of any data, including clinical data, in the prior art regarding the efficacy and safety of 5 mg, 15 mg, 25 mg, 50 mg, 100 mg, 200 mg, or 500 mg of apremilast for the treatment of psoriasis. Alexis Tr. 1818:1-8.

1828. Dr. Alexis claimed that a dose-ranging phase 1 study in the prior art, Wu, disclosed clinical data relating to doses of apremilast greater than 30 mg twice daily. Alexis Tr. 1818:9-14. Phase 1 clinical trials are pharmacology studies, i.e., they generally have nontherapeutic objectives and can be conducted in healthy volunteers. Alexis Tr. 1819:8-24. In other words, phase 1 studies are not efficacy studies. Alexis Tr. 1819:20-24. Phase 2 clinical studies are dose-ranging studies, and are conducted to determine an appropriate dose and dosing regimen for phase 3 clinical trials. Alexis Tr. 1819:25-1820:11. Phase 3 clinical trials are

designed to confirm the preliminary evidence accumulated in phase 2 that a drug is safe and effective for use in the intended indication and recipient population. Alexis Tr. 1820:22-1821:1. Phase 3 studies are carried out to complete the information needed to support adequate instructions for the use of a drug, and is the last phase of the FDA approval process. Alexis Tr. 1821:2-8. Phase 3 trials are expensive and time-consuming. Alexis Tr. 1821:9-12. Dr. Alexis agreed that a pharmaceutical company would not send a drug into phase 3 trials unless they were sure that the dose being tested was the right dose. Alexis Tr. 1821:24-1822:9. Thus, Dr. Alexis acknowledged that Wu did not study the efficacy of apremilast in patients with psoriasis or disclose any information regarding the efficacy of apremilast in patients with psoriasis. Alexis Tr. 1823:20-24, 1824:5-9; JTX-159.

1829. While Dr. Alexis testified that there are allegedly over 70,000 different possibilities of 6-day titration schedules for apremilast, he did not provide any further detail as to what the different permutations could be or provide any data relating to the different titration schedules. Alexis Tr. 1855:10-16. Moreover, one of Dr. Alexis's underlying assumptions is that the doses of apremilast that would have been available in the prior art include multiples of 5 mg (i.e., 5 mg, 15 mg, and 25 mg), based on the teachings of the '536 patent and WO '102. Alexis Tr. 1851:19-25; PDX17-19. However, Dr. Alexis acknowledged that the '536 patent and WO '102 do not disclose any data, including clinical data, regarding the safety and efficacy of apremilast in human patients. Alexis Tr. 1852:1-7. Nor is there any clinical data in the prior art regarding the administration of 5 mg, 15 mg, or 25 mg of apremilast to humans. Alexis Tr. 1853:21-1854:10, 1854:23-1855:9.

1830. Rather, the only data relating to the safety and efficacy of apremilast for the treatment of certain diseases in humans is provided in Papp 2012, Schett 2012, and Pathan 2012.

Alexis Tr. 1852:8-13. And the doses used in Papp 2012 were 10 mg, 20 mg, and 30 mg twice daily, whereas Pathan 2012 administered 30 mg twice daily to patients. Alexis Tr. 1852:14-24.

1831. Another underlying assumption that Dr. Alexis makes is that the duration between dose increments can be even or uneven. Alexis Tr. 1789:14-1790:19; PDX-17-17. However, as Dr. Alexis admitted, the dose increments in Pathan 2012, which used the same titration schedule as in Papp 2012, were increased evenly, every two days. Alexis Tr. 1853:17-20. Thus, Dr. Alexis acknowledged that the number of possibilities would reduce to 18 permutations assuming 10 mg, 20 mg, and 30 mg doses of apremilast and equal dose increments. Alexis Tr. 1856:24-1857:10.

3. A POSA Would Have Reasonably Expected that Titrating the Dose of Apremilast Over 6 Days Would Be Effective in Treating Psoriasis.

1832. It would have required only routine optimization for a POSA to adjust the schedule in Papp 2012 to further mitigate adverse events and arrive at the titration schedule claimed in claims 2, 19, and 21 of the '541 patent. Gilmore Tr. 858:14-17; Alexis Tr. 1812:21-1813:22 (testifying that it is within the skill of a physician to titrate a dose for a patient presenting with psoriasis, and that doing so is a "routine aspect of treating psoriasis with any of those drugs that require dose titration."), 1814:9-13 (agreeing that there is some information about dosing titration of apremilast in the prior art).

1833. There are three primary differences between the titration schedule reported in Papp 2012 and the titration schedule claimed in the asserted claims of the '541 patent. Gilmore Tr. 860:16-861:6. First, the '541 patent starts with a 10 mg morning dose on day 1, which is a lower starting dose than the Papp 2012 schedule, which starts with a 20 mg dose. *Id.* Second, the '541 patent has smaller incremental dose increases of 10 mg, as compared to the 20 mg dose increases in Papp 2012. *Id.; see also* Alexis Tr. 1850:3-7. Third, the goal maintenance dose is

reached on day 6 in the '541 patent, whereas the target maintenance dose was reached on day 5 in Papp 2012. Gilmore Tr. 860:16-861:6; *see also* Alexis Tr. 1847:23-1848:3.

1834. Contrary to Dr. Alexis's claims that these are "notable" differences and that the '541 patent claims a "completely different titration schedule" from Papp 2012 (Alexis Tr. 1850:19-24), Dr. Gilmore testified that each of these three differences are "not life-shattering." Gilmore Tr. 861:7-12. Rather, they are "minor tweaks of routine optimizations to the dosing schedule as displayed in Papp [2012] which was determined to have associated side effects." Gilmore Tr. 861:7-12. As Dr. Gilmore explained, the differences between Papp 2012 and the claimed titration schedule can be analogized to a staircase, where "we know that we are starting at the bottom of the stairs and we know that we want to get to the landing at the top of the flight of the stairs." Gilmore Tr. 861:19-863:4; DDX-4.36. The Papp 2012 study "would be takin the steps two at a time." *Id.* According to Dr. Gilmore, "[y]ou may get to the total accumulative dose a little bit sooner or the top of the landing, but it may be a little bit uncomfortable in doing so, depending on your physical state." *Id.* With the claimed titration schedule, "[y]ou're still trying to get to the landing at the top of the flight of stairs, but you could take the stairs one at a time instead of two at a time." *Id.* As such, it would have been an "obvious adjustment" to slightly decrease the dose increments in Papp 2012 from two steps at a time, i.e., 20 mg per day to one step at a time, i.e., 10 mg per day, to further improve tolerability and make life a little more comfortable for the patient. *Id*.

1835. Even assuming Papp 2012 did not disclose the specific dosing titration schedule used in that study, Dr. Alexis does not dispute that it would have been within the skill of a POSA to optimize the dosing titration schedule as a matter of routine exercise. Alexis Tr. 1813:5-22 ("Q. …It's within the skill of a doctor like you to individually titrate a dose for a patient that's

presented to you with psoriasis; is that right? . . . A. Yes, that [dose titration] would be a routine aspect of treating psoriasis patients with any of those drugs that require dose titration.").

1836. A POSA would have had a reasonable expectation that titrating the dose up to 30 mg BID on day 6 would be successful in treating psoriasis, in light of the teachings of Papp 2012. Gilmore Tr. 859:4-9. In particular, Papp 2012 discloses that 30 mg twice daily was the most effective dose in treating patients with moderate to severe psoriasis. Gilmore Tr. 859:4-9; DTX-153.7; Alexis Tr. 1848:8-25 (admitting that the "efficacy of the maintenance dose of 60 milligrams a day, we are informed of that efficacy by the Papp 2012 article. If the titration schedule is extended by one day . . . I personally would not have the expectation that it would not have efficacy").

1837. Amgen's expert, Dr. Alexis, testified that "it would not have been obvious to the POSA that if you simply extend . . . or the schedule ascribed to Papp, if you simply extend that 5-day titration schedule to 6 days, that there would be a . . . clinically meaningful improvement in tolerability." Alexis Tr. 1849:3-10. However, Dr. Gilmore testified that by slightly slowing down the titration schedule in Papp 2012, a POSA would have reasonably expected that "with the smaller dose increases and getting to the goal dose a bit later," i.e., on day 6, that "this type of optimization, routine optimization, would help to reduce some of the side effects" identified within the first two weeks of treatment in the Papp 2012 study. Gilmore Tr. 859:10-18. Indeed, Dr. Alexis himself agreed that administering 10 mg is giving the patient less drug than 20 mg, and that if "less drug, lower number of milligrams in other words, is administered, I would expect lower rates of adverse -- of some adverse events at least, the ones that are dose dependent." Alexis Tr. 1849:17-1850:2.

1838. As such, asserted claims 2, 19, and 21 of the '541 are obvious over the '536 patent in view of Papp 2012 and Schett 2012. Gilmore Tr. 863:23-864:9.

1839. Contrary to what Amgen might argue, there is nothing special or beneficial about the claimed dosing titration schedule in terms of patient compliance. In fact, Dr. Gilmore testified that when she first used the dosing titration schedule on the Otezla® label, she found that "a significant number of patients" failed "to continue with therapy because of side effects associated with administration" of Otezla®. Gilmore Tr. 876:24-877:11; Alexis Tr. 1858:20-1859:3 (admitting that "there have been post-marketing reports of severe diarrhea, nausea, and vomiting associated with the Otezla," and that the label recommends "dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting); JTX-110.3. In particular, about "40 to 50 percent" of her patents "decided not to continue with treatment" because of the gastrointestinal-related side effects. Gilmore Tr. 877:12-20. Thus, around 2017, after a few years of prescribing the FDA-approved dosing schedule, Dr. Gilmore decided to further extend the titration period because she had "so many patients with side effects that they found intolerable." Gilmore Tr. 947:16-948:11. To be clear, Dr. Gilmore's extended titration schedule for apremilast was not taught in the prior art as of 2014. Gilmore Tr. 948:20-23; Alexis Tr. 1844:22-25.

1840. Dr. Gilmore's post-marketing experience with Otezla® is consistent with reports that Celgene and Amgen received in the field from other physicians. For example, a November 10, 2014 e-mail indicates that the marketing team at Celgene held a brainstorming meeting to discuss tolerability management because of side effects reported for Otezla®, e.g., nausea and diarrhea. JTX-97; Kim Tr. 1640:25-1641:4. Amgen's 30(b)(6) marketing witness, Dr. Susan

Kim, testified that one of the options that Celgene discussed for managing tolerability was extending the titration schedule. Kim Tr. 1641:5-9; JTX-97.

1841. A November 13, 2014 e-mail provides that as a result of that brainstorming meeting, "US marketing will continue to assess significance / impact of tolerability profile in the market – based on analysis, we will revisit the rationale / business case for a 'prevention' approach." JTX-123; Kim Tr. 1641:10-1642:1. Dr. Kim testified that the U.S. marketing group at Celgene continued to assess the tolerability profile of Otezla® because "GI tolerability is one of the side effects." Kim Tr. 1642:2-8.

1842. A Celgene document summarizing information received from advisory boards relating to the dose titration schedule of Otezla® provides that "[m]any advisors adjust the dose of Otezla to alleviate tolerability issues." JTX-98.4; Alexis Tr. 1859:25-1860:12. As Amgen's 30(b)(6) marketing witness, Dr. Kim, testified, advisory boards are meetings held with key opinion leaders or physicians "who are experienced in using Otezla." Kim Tr. 1643:5-11.

1843. Physicians also reported to Celgene that the use of "2 titration packs concurrently in order to more gradually increase dosage can reduce tolerability issues." JTX-98.4; Alexis Tr. 1860:13-16. The Rheumatology Advisory Board in Fort Lauderdale, Florida further told Celgene that "[d]ue to the number of gastrointestinal AEs observed, a doctor in one advisor's practice has been prescribing up to 3 titration packs to patients." JTX-98.4; Alexis Tr. 1860:17-25. In the same document, a Maui Derm Advisory Board noted to Celgene that "they use more than one starter pack," with one advisor commenting that "they use several starter packs and may not even reach the BID dose if patients are achieving skin clearance (which some are) on the QD [once a day] dose with no tolerability issues." JTX-98.11; Alexis Tr. 1861:5-13.

1844. In December 2017, there was an internal meeting at Celgene regarding the dose titration of Otezla®, in which they discussed a document titled "Titration Evaluation." JTX-99.1; Alexis Tr. 1861:21-1862:6. The Celgene document provides that "GI tolerability is a major clinical barrier to starting and keeping patients on Otezla." JTX-100.25; Alexis Tr. 1862:23-1863:4; Kim Tr. 1648:25-1649:4 ("GI tolerability is one of the barriers"). Celgene reports that "[d]iarrhea typically occurs to patients experiencing improvement of symptoms," and that "[d]iarrhea can often lead to discontinuation." *Id.* As such, Celgene recognized that "[t]o improve compliance, many physicians extend titration schedule in starter pack or recommend concomitant therapy for diarrhea." JTX-100.25; Alexis Tr. 1863:5-9; Kim Tr.1649:5-10. Celgene also received feedback from key opinion leaders on titration variations, in which "[b]oth rheumatologists and dermatologists have proactively reported modifying titration to mitigate GI tolerability." JTX-100.26; Kim Tr. 1648:2-5. According to Celgene, these physicians "are often providing patients with two titration packs and are suggesting that patients double the length of time to achieve the full 30mg BID dose," and "are also giving one titration pack and then suggesting that patients titrate up to 30 mg QD for a length of time before moving to 30 mg BID." JTX-100.26; Alexis Tr. 1863:18-1864:2; Kim Tr. 1648:6-19 ("this is a summary of physicians telling us how they modify titration").

4. The Remaining Limitations in Claim 21 of the '541 Patent Would Have Been Obvious.

1845. Asserted claim 21 of the '541 patent requires that apremilast is administered in tablet form. JTX-13.22 (claim 21). As discussed above, Papp 2012 disclosed the administration of apremilast to patients with psoriasis in 10 mg, 20 mg, and 30 mg tablets. DTX-153.2; Gilmore Tr. 840:14-841:3. In addition, claim 1 of the '536 patent teaches a POSA a method of treating psoriasis using stereomerically pure apremilast in dose ranges of about 10 mg to 200 mg

per day in tablet or capsule form as either a single dose or a divided dose. JTX-7.20-21 (claim 1); Gilmore Tr. 833:21-834:1. Thus, claim 21 would have been obvious over the '536 patent in view of Papp 2012 and Schett 2012.

5. Amgen Asserts No Objective Indicia Of Nonobviousness.

1846. During prosecution of the '541 patent, the examiner rejected the claims as obvious under 35 U.S.C. § 103 over the '536 patent in view of Papp 2012 and Schett 2012. JTX-24.768-777. The examiner found that the "prior art references in combination discloses the general conditions of the claimed invention (initial dose titration with three different dosages in escalating amounts for providing apremilast in the treatment of the same disorder)." JTX-24.774. In addition, "dose escalation or titration is a well-known technique to find out optimal dosages while easing a patient into a course of treatment and the dosage of an active ingredient and administration schedule is known to be a result-effective variable." *Id.* Further, "the initial dose escalation or titration for decreasing adverse events (AEs) related to treatment initiation of apremilast was known in the art as evidenced by Schett [2012] and Papp [2012]." *Id.* As such, the examiner concluded that "it would have been obvious for the skilled artisan to use a little more gradual escalation scheme for reducing the occurrences of adverse events than that of Papp [2012]." *Id.* The examiner noted that "[d]etermining optimum dosages and dosage schedules is a routine medical procedure." JTX-24.774-775. Thus, "[i]n the absence of the unexpected result from the claimed parameter, the optimization of dosing amount and titration period would have been obvious at the time of applicant's invention." JTX-24.775.

1847. In response, Celgene argued that "even assuming, *arguendo*, that a case of *prima facie* case of obviousness has been established by the Office, with which Applicant disagrees, the evidence of unexpected results attached hereto rebuts any *prima facie* case of obviousness." JTX.24-800; Scharfstein Tr. 973:16-24. As evidence of unexpected results, Celgene compared

the results from two studies—Kavanaugh and Papp 2012. JTX.24-800; Scharfstein Tr. 973:25-974:15. In Kavanaugh, apremilast was dose-titrated according to the claimed titration schedule. JTX-24.800; Scharfstein Tr. 973:25-974:15. Celgene told the Patent Office that "Kavnaugh reported that 61.3% of patients administered 30 mg of apremilast twice per day (BID) suffered an adverse event, and 7.1% of patients withdrew from the study due to adverse events." *Id.* Celgene contrasted the results in Kavanaugh to Papp 2012, which Celgene claimed "discloses that 82% of patients suffered an adverse event, and 11% of the patients needed to withdraw from the study due to adverse events." *Id.*

1848. Defendants' expert Dr. Scharfstein testified that the analysis Celgene presented to the Patent Office regarding the differences in adverse events and withdrawals between Kavanaugh and Papp 2012 was significantly flawed. Scharfstein Tr. 980:14-986:21. As an initial matter, Dr. Scharfstein testified that it is not statistically valid to look at the differences in adverse events between the treatment groups and conclude that the difference is due to the dosing titration schedules used in Kavanaugh and Papp 2012, as Celgene had represented to the PTO. Scharfstein Tr. 967:24-968:12. Such an analysis ignores "the fact that there can be differences across the two groups with respect to the background or control group adverse event group." *Id.*

1849. Celgene further claimed that these differences "remain[] when baseline rates of adverse events are accounted for." JTX-24.800; Scharfstein Tr. 975:21-976:7. In other words, Celgene argued that the differences in adverse events and withdrawals between Kavanaugh and Papp 2012 remain when the control group is subtracted out. Scharfstein Tr. 975:21-976:7. In particular, Celgene represented that "[a] comparison of the difference in baseline adverse events demonstrated an unexpected result: patients receiving the titration dosing as in instant claim 1

experience only a 13.1% increase in adverse events; in contrast, patients receiving the titration dosing as in Papp experience a 17% increase in adverse events." JTX-24.800-801; Scharfstein Tr. 976:8-14. Celgene told the patent office that such evidence of unexpected results "should establish that 'the differences in results are in fact unexpected and unobvious and of both statistical and practical significance.'" JTX-24.803.

1850. At around the same time the '541 patent was in front of the patent office, Celgene was also prosecuting the '854 patent before the same examiner, which claims the same dosing titration schedule as the '541 patent but for a different indication—psoriatic arthritis. Scharfstein Tr. 978:24-979:22. During prosecution of the '854 patent, Celgene submitted the exact same evidence of unexpected results, and relied on the exact same analysis as with the '541 patent prosecution. Scharfstein Tr. 980:2-6; JTX-23.699-702. Celgene told the patent office that the difference in baseline adverse events (i.e., subtracting out the control group) between Kavanaugh (13.1%) and Papp 2012 (17%) was "statistically significant." JTX-23.700; Scharfstein Tr. 980:7-11.

1851. After Celgene made these claims of "statistically significant" unexpected results, the examiner withdrew his obviousness rejections of the '541 and '854 patent claims over the '536 patent, Papp 2012, and Schett 2012. JTX-24.1083; JTX-23.710-714.

1852. As Dr. Scharfstein testified, however, even when comparing the treatment effect (i.e., the treatment group minus the control group) between two studies, such an analysis has to be done carefully because there might be significant differences in the study design that could skew the results. Scharfstein Tr. 969:6-970:5. While there are a series of statistical tests that could be done to determine whether the difference in treatment effect is "consistent with there being no difference in the treatment's effect across studies," these tests can only be performed

under the assumption that the "two studies are identical to one another." Scharfstein Tr. 969:13-24. With respect to the Kavanaugh and Papp 2012 studies, Dr. Scharfstein testified that this was not a fair assumption to make, because there "are very key differences between the studies" that need to be "take[n] into consideration when doing these statistical tests." Scharfstein Tr. 986:4-21.

1853. For example, Dr. Scharfstein explained that there were significant differences with respect to the timing and collection of adverse events between Kavanaugh and Papp 2012. Scharfstein Tr. 986:23-987:2; DDX5-35. In Kavanaugh, data on adverse events were collected at 4 weeks, 16 weeks, and 24 weeks during the treatment period, whereas adverse events in Papp were collected more than dozen times during the treatment period, with the largest difference between assessments being two weeks. Scharfstein Tr. 987:9-988:10; DDX5-35. Such a difference in the timing of collecting data on adverse events could have an impact on adverse event reporting because a patient might not remember if they suffered any adverse events over a longer period of time, such as in Kavanaugh. Scharfstein Tr. 988:11-16.

1854. Another key difference between the Kavanaugh and Papp 2012 studies was the indication being studied. Scharfstein Tr. 988:18-989:12. Kavanaugh was studying the efficacy and safety of apremilast in patients with psoriatic arthritis, whereas the disease state being studied in Papp 2012 was psoriasis. *Id.* These differences in the disease state could affect the reporting of adverse events, including the type of adverse events that patients are suffering and the frequency of adverse events. Scharfstein 989:13-20.

1855. Dr. Scharfstein testified that another difference between Kavanaugh and Papp 2012 was the severity of psoriasis. Scharfstein Tr. 989:24-991:16. Patients enrolled in the Kavanaugh study has less severe disease than in Papp 2012, as indicated by the PASI scores and

body surface area impacted by psoriasis. *Id.* Depending on the severity of the disease, patients could report adverse events differently, which could impact the findings of any cross-study comparison. Scharfstein Tr. 991:17-992:1.

1856. A final key difference between the Kavanaugh and Pap 2012 studies was the geographic location of the patients. Scharfstein Tr. 992:2-11. The Kavanaugh study was conducted in 83 sites in 13 countries, whereas Papp 2012 was conducted in 35 sites in the U.S. and Canada. *Id.* According to Dr. Scharfstein, the degree to which geography impacts the occurrence of adverse events and the degree to which treatment effects might vary by geographic region could impact the findings of any cross-study comparison. Scharfstein Tr. 992:12-18.

1857. Even assuming that the Kavanaugh and Papp 2012 studies were identical in design, Dr. Scharfstein conducted a statistical analysis and found that there were no statistically significant differences in the incidence of adverse events. Scharfstein Tr. 980:12-16. In particular, he compared the incidence of adverse events in the 30 mg BID arm in Kavanaugh, which reported a treatment effect of 13.1%, and the 30 mg BID arm in Papp 2012, which reported a treatment effect of 17%, and found that the difference of 4% between the two studies was not statistically significant. Scharfstein Tr. 980:21-981:9.

1858. Dr. Scharfstein also compared the incidence of adverse events in the 20 mg BID treatment arm in Kavanaugh, which reported a treatment effect of 12%, and the 20 mg BID treatment arm in Papp 2012, which reported a treatment effect of 12%, and found that the difference of 0% was not statistically significant. Scharfstein Tr. 981:16-25.

1859. Dr. Scharfstein compared the incidence of adverse events in the 20 mg BID treatment arm in Kavanaugh, which reported a treatment effect of 12%, and the 20 mg BID

treatment arm in Schett 2012, which reported a treatment effect of 5%, and found that the difference of -7% was not statistically significant. Scharfstein Tr. 982:5-13.

1860. Dr. Scharfstein compared the incidence of adverse events in the 20 mg BID treatment arm in Kavanaugh, which reported a treatment effect of 12%, and the 40 mg QD treatment arm in Schett 2012, which reported a treatment effect of 6%, and found that the difference of -6% was not statistically significant. Scharfstein Tr. 982:14-983:2.

1861. Dr. Scharfstein further conducted a statistical analysis comparing the incidence of withdrawals between Kavanaugh and Papp 2012 and found that there were no statistically significant differences. Scharfstein Tr. 984:7-12.

1862. Dr. Scharfstein compared the number of withdrawals in the 30 mg BID treatment arm in Kavanaugh, which reported a treatment effect of 2%, and the 30 mg BID treatment arm in Papp 2012, which reported a treatment effect of 6%, and found that the difference of about 3% was not statistically significant. Scharfstein Tr. 984:16-25.

1863. Dr. Scharfstein compared the number of withdrawals in the 20 mg BID treatment arm in Kavanaugh, which reported a treatment effect of 1%, and the 20 mg BID treatment arm in Papp 2012, which reported a treatment effect of 4%, and found that the difference of about 2% was not statistically significant. Scharfstein Tr. 985:6-12.

1864. Dr. Scharfstein compared the number of withdrawals in the 20 mg BID treatment arm in Kavanaugh, which reported a treatment effect of 1%, and the 20 mg BID treatment arm in Schett 2012, which reported a treatment effect of 4%, and found that the difference of 3% was not statistically significant. Scharfstein Tr. 985:16-21.

1865. Dr. Scharfstein compared the number of withdrawals in the 20 mg BID treatment arm in Kavanaugh, which reported a treatment effect of 1%, and the 40 mg QD treatment arm in

Schett 2012, which reported a treatment effect of 6%, and found that the difference of 5% was not statistically significant. Scharfstein Tr. 985:22-986:3.

1866. As such, Dr. Scharfstein concluded that he has not seen any statistically reliable evidence to suggest that there is a difference between the claimed titration schedule and Papp 2012 with respect to adverse events. Scharfstein Tr. 992:19-25.

1867. Amgen's Response to Defendants' Joint Invalidity Contentions relied on substantially the same evidence and analysis that Celgene presented to the Patent Office to argue that objective indicia, primarily unexpected results, supported the nonobviousness of the asserted claims of the '541 patent. *See* Dkt. No. 373 at 3. During expert discovery, however, Amgen represented that it would no longer be asserting a theory of objective indicia, including unexpected results, for the asserted claims of the '541 patent. *Id.*

1868. Nevertheless, Amgen submitted a "rebuttal" report from Dr. Thisted, who opined that the claimed titration schedule was associated with a lower incidence of adverse events and withdrawals than the prior art titration schedule in Papp 2012, and relied on the same evidence of unexpected results for the '541 patent, including the same evidence presented to the PTO, that Amgen previously represented it would not assert. *See* Dkt. No. 353 at 4. Dr. Alexis relied on Dr. Thisted's analysis to opine that the differences in the incidence of adverse events and withdrawals between the claimed and prior art titration schedules were clinically meaningful and provided a real benefit to patients. *Id.*

1869. As a result, Defendants filed a motion *in limine* to preclude Dr. Thisted from testifying at trial and to preclude Dr. Alexis from offering certain testimony at trial that relies on Dr. Thisted's opinions. *See* Dkt. 352-353. This Court held that "Amgen may not go back on its word" regarding unexpected results "without prejudicing Defendants who would otherwise not

be able to produce rebuttal evidence on this theory." Dkt. 405 at 17. Nevertheless, the Court stated that it would consider Dr. Alexis and Dr. Thisted's opinions "to the extent they seek to rebut Defendants' *prima facie* obviousness case." *Id.*

1870. At trial, Amgen did not present any evidence related to any alleged objective indicia of nonobviousness with respect to claims 2, 19, and 21 of the '541 patent. Nor did Amgen present any testimony from Dr. Thisted or Dr. Alexis regarding how the incidence of adverse events and withdrawals was improved with the claimed titration schedule over Papp 2012.

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CERTIFICATION OF SERVICE

The undersigned attorney certifies that a copy of the foregoing **DEFENDANTS' PROPOSED FINDINGS OF FACT** was served by notice of electronic filing on the 8th day of July 2021, upon all counsel of record.

Dated: July 8, 2021

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